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=> s phosphodiesterase inhibitor or PDE inhibitor
L1       28764 PHOSPHODIESTERASE INHIBITOR OR PDE INHIBITOR

=> s stroke
L2      367169 STROKE

=> s l1 and l2
L3         798 L1 AND L2

=>  s l3 and py<2000
   2 FILES SEARCHED...
L4         403 L3 AND PY<2000

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5          320 DUP REM L4 (83 DUPLICATES REMOVED)

=> s cognitive or cognition
L6      238727 COGNITIVE OR COGNITION

=> s l5 and l6
L7          21 L5 AND L6

=> d l7 1-21

L7   ANSWER 1 OF 21  USPATFULL
AN     2001:202586  USPATFULL
TI     Methods for treating an ischemic disorder and improving stroke
       outcome
IN     Pinsky, David J., Riverdale, NY, United States
       Stern, David, Great Neck, NY, United States
       Schmidt, Ann Marie, Franklin Lakes, NJ, United States
       Rose, Eric A., Tenafly, NJ, United States
       Connolly, E. Sander, New York, NY, United States
       Solomon, Robert A., Palisades, NY, United States
       Prestigiacomo, Charles J., Teaneck, NJ, United States
PA     The Trustees of Columbia University in the City of New York, New York,
       NY, United States (U.S. corporation)
PI     US 6316403         B1   20011113
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WO 9813058 19980402
AI US 1999-269426 19990625 (9)
WO 1997-US17229 19970925
19990625 PCT 371 date
19990625 PCT 102(e) date
RLI Continuation-in-part of Ser. No. US 1996-721447, filed on 27 Sep 1996, now abandoned
DT Utility
FS GRANTED
LN.CNT 5590
INCL INCLM: 514/002.000
INCLS: 514/021.000
NCL NCLM: 514/002.000
NCLS: 514/021.000
IC [7]
ICM: A61K038-00
EXF 514/23; 514/20; 514/2; 514/21
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 2 OF 21 USPATFULL
AN 2000:142387 USPATFULL
TI Naphthyridine derivatives
IN Hersperger, Rene, Munchenstein, Switzerland
PA Novartis AG, Basel, Switzerland (non-U.S. corporation)
PI US 6136821 20001024
WO 9818796 19980507 <--
AI US 1999-297245 19990427 (9)
WO 1997-EP5898 19971024
19990427 PCT 371 date
19990427 PCT 102(e) date
PRAI GB 1996-22386 19961028
DT Utility
FS Granted
LN.CNT 1028
INCL INCLM: 514/300.000
INCLS: 546/122.000
NCL NCLM: 514/300.000
NCLS: 546/122.000
IC [7]
ICM: A61K031-435
ICS: C07D471-04
EXF 546/122; 514/303
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 3 OF 21 USPATFULL
AN 2000:142377 USPATFULL
TI Pyrido[2,3-D]pyrimidine derivatives and pharmaceutical compositions thereof
IN Takayama, Kazuhisa, Ibaraki, Japan
Hisamichi, Hiroyuki, Ibaraki, Japan
Iwata, Masahiro, Ibaraki, Japan
Kubota, Hideki, Ibaraki, Japan
Aoki, Motonori, Ibaraki, Japan
PA Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan (non-U.S. corporation)
PI US 6136810 20001024
WO 9719078 19970529 <--
AI US 1998-66370 19980430 (9)
WO 1996-JP3389 19961120
19980430 PCT 371 date

19980430 PCT 102(e) date
PRAI JP 1995-303065 19951121
JP 1996-7725 19960119
JP 1996-43853 19960229
JP 1996-141868 19960604
DT Utility
FS Granted
LN.CNT 2605
INCL INCLM: 514/258.000
INCLS: 546/279.000
NCL NCLM: 514/264.100
NCLS: 544/279.000
IC [7]
ICM: A61K031-505
ICS: C07D471-04
EXF 544/279; 514/258
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 4 OF 21 USPATFULL
AN 2000:91972 USPATFULL
TI Phenylpyridine derivatives useful as **phosphodiesterase inhibitors**
IN Manley, Paul W., Arlesheim, Switzerland
PA Novartis AG, Basel, Switzerland (non-U.S. corporation)
PI US 6090817 20000718
WO 9732853 19970912
AI US 1998-142099 19980901 (9)
WO 1997-EP1157 19970307
19980901 PCT 371 date
19980901 PCT 102(e) date
PRAI GB 1996-4926 19960308
DT Utility
FS Granted
LN.CNT 1144
INCL INCLM: 514/277.000
INCLS: 546/268.400; 546/118.000; 546/296.000; 546/303.000; 514/359.000; 514/379.000; 514/188.000
NCL NCLM: 514/277.000
NCLS: 514/188.000; 514/359.000; 514/379.000; 546/118.000; 546/268.400; 546/296.000; 546/303.000
IC [7]
ICM: A61K031-655
ICS: A61K031-371; A61K031-41; C07D413-10; C07D407-10
EXF 546/329; 546/346; 546/280.1; 546/280.4; 546/268.1; 546/290; 546/268.4; 546/296; 546/307; 546/301; 546/303; 546/118; 514/188; 514/202; 514/222.2; 514/226.2; 514/233.5; 514/277; 514/359; 514/379
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 5 OF 21 USPATFULL
AN 1999:141942 USPATFULL
TI Substituted xanthines and their use in the treatment of cerebrovascular disorders and other diseases
IN Spicer, Barbara Ann, Epsom, United Kingdom
Smith, Harry, Epsom, United Kingdom
Maschler, Harald, Nordstremmen, Germany, Federal Republic of
PA SmithKline Beecham p.l.c., Brentford, United Kingdom (non-U.S. corporation)
PI US 5981535 19991109 <--
AI US 1995-474093 19950607 (8)
RLI Continuation of Ser. No. US 1995-379092, filed on 26 Jan 1995, now

abandoned which is a continuation of Ser. No. US 1993-28765, filed on 9 Mar 1993, now abandoned which is a continuation of Ser. No. US 1990-497992, filed on 23 Mar 1990, now abandoned
PRAI GB 1989-6792 19890323
DT Utility
FS Granted
LN.CNT 1178
INCL INCLM: 514/263.000
INCLS: 544/118.000; 544/271.000; 544/272.000; 544/267.000
NCL NCLM: 514/263.340
NCLS: 544/118.000; 544/267.000; 544/271.000; 544/272.000
IC [6]
ICM: A61K031-52
ICS: C07D473-06
EXF 514/263; 514/234.2; 544/118; 544/271; 544/272; 544/267
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 6 OF 21 USPATFULL
AN 1998:122421 USPATFULL
TI Naphthyridine derivatives and pharmaceutical compositions thereof
IN Takayama, Kazuhisa, Ibaraki, Japan
Iwata, Masahiro, Ibaraki, Japan
Okamoto, Yoshinori, Ibaraki, Japan
Aoki, Motonori, Ibaraki, Japan
Niwa, Akira, Chiba, Japan
Isomura, Yasuo, Ibaraki, Japan
PA Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan (non-U.S. corporation)
PI US 5817670 19981006 <--
WO 9606843 19960307 <--
AI US 1997-776295 19970130 (8)
WO 1995-JP1700 19950828
19970130 PCT 371 date
19970130 PCT 102(e) date
PRAI JP 1994-203677 19940829
JP 1995-19113 19950207
DT Utility
FS Granted
LN.CNT 2569
INCL INCLM: 514/300.000
INCLS: 546/122.000; 546/123.000
NCL NCLM: 514/300.000
NCLS: 546/122.000; 546/123.000
IC [6]
ICM: A61K031-435
ICS: C07D471-04
EXF 546/122; 546/123; 514/300
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 7 OF 21 USPATFULL
AN 1998:75569 USPATFULL
TI A3 adenosine receptor agonists
IN Jacobson, Kenneth A., Silver Spring, MD, United States
Gallo-Rodriguez, Carola, Buenos Aires, Argentina
van Galen, Philip J. M., Oss, Netherlands
von Lubitz, Dag K. J. E., Alexandria, VA, United States
Jeong, Heaok Kim, Rockville, MD, United States
PA The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
PI US 5773423 19980630 <--

AI US 1994-274628 19940713 (8)
RLI Continuation-in-part of Ser. No. US 1993-163324, filed on 6 Dec 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-91109, filed on 13 Jul 1993, now abandoned
DT Utility
FS Granted
LN.CNT 4850
INCL INCLM: 514/045.000
INCLS: 514/046.000; 536/027.220; 536/027.600; 536/027.630
NCL NCLM: 514/045.000
NCLS: 514/046.000; 536/027.220; 536/027.600; 536/027.630
IC [6]
ICM: A61K031-70
EXF 536/27.22; 536/27.6; 536/27.63; 514/45; 514/46
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 8 OF 21 USPATFULL
AN 1998:48424 USPATFULL
TI Isoquinoline compounds, compositions containing them and their pharmaceutical uses
IN Naef, Reto, Rheinfelden, Switzerland
PA Novartis AG, Basel, Switzerland (non-U.S. corporation)
PI US 5747506 19980505 <--
AI US 1996-771556 19961220 (8)
RLI Continuation of Ser. No. US 1995-472042, filed on 6 Jun 1995, now abandoned which is a continuation of Ser. No. US 1994-333699, filed on 3 Nov 1994, now abandoned
PRAI GB 1993-22828 19931105
DT Utility
FS Granted
LN.CNT 873
INCL INCLM: 514/307.000
INCLS: 546/144.000
NCL NCLM: 514/307.000
NCLS: 546/144.000
IC [6]
ICM: C07D217-16
ICS: A61K031-47
EXF 546/144; 514/307
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 9 OF 21 USPATFULL
AN 1998:34066 USPATFULL
TI 8-substituted xanthine derivatives and method of use thereof
IN Spicer, Barbara Ann, Epsom, England
Smith, Harry, Epsom, England
Maschler, Harald, Nordstemmen, Germany, Federal Republic of
PA Beecham Group, Brentford, United Kingdom (non-U.S. corporation)
PI US 5734051 19980331 <--
AI US 1995-477157 19950607 (8)
RLI Division of Ser. No. US 1995-379092, filed on 26 Jan 1995, now abandoned which is a continuation of Ser. No. US 1993-28765, filed on 9 Mar 1993, now abandoned which is a continuation of Ser. No. US 1990-497992, filed on 23 Mar 1990, now abandoned
PRAI GB 1989-6792 19890323
DT Utility
FS Granted

LN.CNT 1082
INCL INCLM: 544/118.000
INCLS: 544/267.000; 544/271.000; 544/272.000
NCL NCLM: 544/118.000
NCLS: 544/267.000; 544/271.000; 544/272.000
IC [6]
ICM: C07D473-06
ICS: C07D473-04; A61K031-52; A61K031-535
EXF 544/271; 544/272; 544/267; 544/118
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 10 OF 21 USPATFULL
AN 96:72899 USPATFULL
TI Imidazole 5-position substituted angiotensin II antagonists
IN Duncia, John J. V., Wilmington, DE, United States
Ensinger, Carol L., Newark, DE, United States
Olson, Richard E., Wilmington, DE, United States
Quan, Mimi L., Newark, DE, United States
Santella, III, Joseph B., Springfield, PA, United States
Vanatten, Mary K., Wilmington, DE, United States
PA The DuPont Merck Pharmaceutical Company, Wilmington, DE, United States (U.S. corporation)
PI US 5545651 19960813 <--
AI US 1994-348843 19941128 (8)
RLI Division of Ser. No. US 1993-72977, filed on 10 Jun 1993, now patented, Pat. No. US 5395844
DT Utility
FS Granted
LN.CNT 5010
INCL INCLM: 514/381.000
INCLS: 514/235.800; 514/307.000; 514/314.000; 514/326.000; 514/333.000; 514/341.000; 514/359.000; 514/383.000; 514/397.000; 514/398.000; 514/399.000; 514/400.000; 544/139.000; 546/148.000; 546/174.000; 546/176.000; 546/180.000; 546/210.000; 546/256.000; 546/272.400; 546/272.700; 546/274.400; 546/274.700; 546/275.100; 546/022.000; 546/023.000; 546/024.000; 548/253.000; 548/255.000; 548/261.000; 548/266.200; 548/315.100; 548/335.100; 548/341.100; 548/343.100; 548/343.500; 548/346.100; 548/314.700
NCL NCLM: 514/381.000
NCLS: 514/235.800; 514/307.000; 514/314.000; 514/326.000; 514/333.000; 514/341.000; 514/359.000; 514/383.000; 514/397.000; 514/398.000; 514/399.000; 514/400.000; 544/139.000; 546/022.000; 546/023.000; 546/024.000; 546/148.000; 546/174.000; 546/176.000; 546/180.000; 546/210.000; 546/256.000; 546/272.400; 546/272.700; 546/274.400; 546/274.700; 546/275.100; 548/253.000; 548/255.000; 548/261.000; 548/266.200; 548/314.700; 548/315.100; 548/335.100; 548/341.100; 548/343.100; 548/343.500; 548/346.100
IC [6]
ICM: C07D401-14
ICS: A61K031-415
EXF 546/207; 546/210; 546/256; 546/276; 546/148; 546/180; 546/174; 546/176; 548/387; 548/253; 548/315.1; 548/319.7; 548/335.1; 548/341.1; 548/343.5;
548/346.1; 548/255; 548/261; 548/266.2; 548/343.1; 514/326; 514/333; 514/341; 514/381; 514/396; 514/398; 514/399; 514/400; 514/397; 514/235.8; 514/307; 514/314; 514/383; 514/359; 544/139
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 11 OF 21 USPATFULL
AN 95:36408 USPATFULL

TI Xanthine derivatives
IN Smith, David G., SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epson, Surrey, England
Buckle, Derek R., SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epson, Surrey, England
Fenwick, Ashley E., SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epson, Surrey, England KT18 5XQ
PI US 5409934 19950425 <--
WO 9211260 19920709 <--
AI US 1993-78152 19930707 (8)
WO 1991-GB2286 19911219
19930707 PCT 371 date
19930707 PCT 102(e) date
PRAI GB 1990-27752 19901221
GB 1990-27899 19901221
DT Utility
FS Granted
LN.CNT 1348
INCL INCLM: 514/263.000
INCLS: 514/826.000; 544/267.000; 544/268.000; 544/272.000
NCL NCLM: 514/263.330
NCLS: 514/263.200; 514/263.340; 514/826.000; 544/267.000; 544/268.000; 544/272.000
IC [6]
ICM: C07D473-06
ICS: C07D473-10; A61K031-52
EXF 544/267; 544/268; 544/272; 514/263
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 12 OF 21 USPATFULL
AN 95:20736 USPATFULL
TI Imidazole 5-position substituted angiotensin II antagonists
IN Duncia, John J. V., Wilmington, DE, United States
Ensinger, Carol L., Newark, DE, United States
Olson, Richard E., Wilmington, DE, United States
Quan, Mimi L., Newark, DE, United States
Santella, III, Joseph B., Springfield, PA, United States
Vanatten, Mary K., Wilmington, DE, United States
PA The Du Pont Merck Pharmaceutical Company, Wilmington, DE, United States (U.S. corporation)
PI US 5395844 19950307 <--
AI US 1993-72977 19930610 (8)
DT Utility
FS Granted
LN.CNT 5135
INCL INCLM: 514/333.000
INCLS: 546/207.000; 546/210.000; 546/256.000; 546/276.000; 548/253.000; 548/314.700; 548/315.100; 548/335.100; 548/341.500; 548/343.500; 548/346.100; 514/326.000; 514/341.000; 514/381.000; 514/396.000; 514/397.000; 514/399.000; 514/400.000
NCL NCLM: 514/333.000
NCLS: 514/326.000; 514/341.000; 514/381.000; 514/396.000; 514/397.000; 514/399.000; 514/400.000; 544/139.000; 544/333.000; 544/405.000; 546/022.000; 546/023.000; 546/146.000; 546/147.000; 546/174.000; 546/207.000; 546/210.000; 546/256.000; 546/272.400; 546/274.400; 546/274.700; 546/275.100; 548/253.000; 548/314.700; 548/315.100; 548/335.100; 548/341.500; 548/343.500; 548/346.100
IC [6]
ICM: A61K031-415

ICS: C07D401-14; C07D403-02
EXF 548/387; 548/253; 548/319.7; 548/315.1; 548/341.5; 548/335.1; 548/343.5;
548/346.1; 514/396; 514/398; 514/326; 514/341; 514/333; 514/381; 514/397; 514/399; 514/400; 546/207; 546/210; 546/256; 546/276
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 13 OF 21 USPATFULL
AN 94:113029 USPATFULL
TI Angiotension-II receptor blocking, azacycloalkyl or azacycloalkenyl
IN Duncia, John J. V., Wilmington, DE, United States
PA The Du Pont Merck Pharmaceutical Company, Wilmington, DE, United States (U.S. corporation)
PI US 5376666 19941227 <--
AI US 1992-983307 19921130 (7)
DT Utility
FS Granted
LN.CNT 1597
INCL INCLM: 514/303.000
INCLS: 514/212.000; 514/235.800; 514/236.200; 514/326.000; 514/341.000; 514/381.000; 514/397.000; 540/603.000; 544/131.000; 546/210.000; 546/276.000; 546/278.000; 546/118.000; 548/252.000; 548/253.000; 548/254.000; 548/314.700
NCL NCLM: 514/303.000
NCLS: 514/080.000; 514/217.050; 514/217.070; 514/217.090; 514/235.800; 514/236.200; 514/326.000; 514/341.000; 514/381.000; 514/397.000; 540/603.000; 544/131.000; 546/118.000; 546/210.000; 546/274.400; 546/274.700; 548/252.000; 548/253.000; 548/254.000; 548/314.700
IC [5]
ICM: A61K031-44
ICS: C07D471-04; C07D211-78
EXF 540/603; 546/210; 546/276; 546/278; 546/118; 548/252; 548/253; 548/254; 548/314.7; 544/131; 514/212; 514/235.8; 514/236.2; 514/303; 514/326; 514/341; 514/381; 514/397
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 14 OF 21 USPATFULL
AN 94:97751 USPATFULL
TI Phenyl-substituted cycloalkenyl compounds useful as PDE IV inhibitors
IN Maschler, Harald, Nordstemmen, Germany, Federal Republic of
Christensen, IV, Siegfried B., King of Prussia, PA, United States
PA SmithKline Beecham Pharma GmbH, Munich, Germany, Federal Republic of (non-U.S. corporation)
SmithKline Beecham Corporation, King of Prussia, PA, United States (U.S.
corporation)
PI US 5362915 19941108 <--
WO 9115451 19911017 <--
AI US 1992-934546 19921002 (7)
WO 1991-EP637 19910402
19921002 PCT 371 date
19921002 PCT 102(e) date
PRAI GB 1990-7762 19900405
DT Utility
FS Granted
LN.CNT 1007
INCL INCLM: 568/020.000
INCLS: 568/042.000; 568/049.000; 568/052.000; 568/329.000; 568/330.000; 568/644.000
NCL NCLM: 568/020.000

NCLS: 568/042.000; 568/049.000; 568/052.000; 568/329.000; 568/330.000; 568/644.000
IC [5]
ICM: C07C043-205
ICS: A61K031-075
EXF 568/644; 568/20; 568/42; 568/49; 568/52; 568/329; 568/330; 514/719; 514/683; 514/684; 514/706; 514/712
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 15 OF 21 USPATFULL
AN 94:51416 USPATFULL
TI Xanthines
IN Maschler, Harald, Gronau, Germany, Federal Republic of
Wilke, Rolf T., Gronau, Germany, Federal Republic of
Jukna, Johannes, Gronau, Germany, Federal Republic of
PA Beecham-Wuelfing GmbH & Co.K.G., Germany, Federal Republic of (non-U.S. corporation)
PI US 5321029 19940614 <--
AI US 1992-821333 19920113 (7)
RLI Continuation of Ser. No. US 1991-634978, filed on 7 Jan 1991, now abandoned which is a continuation of Ser. No. US 1989-436233, filed on 14 Nov 1989, now abandoned
PRAI GB 1988-265954 19881114
DT Utility
FS Granted
LN.CNT 1131
INCL INCLM: 514/263.000
INCLS: 514/265.000; 544/267.000; 544/271.000; 544/273.000
NCL NCLM: 514/263.360
NCLS: 514/263.340; 544/267.000; 544/271.000; 544/273.000
IC [5]
ICM: A61K031-52
ICS: C07D473-06
EXF 514/263; 514/265; 544/267; 544/271; 544/273
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 16 OF 21 USPATFULL
AN 94:37943 USPATFULL
TI Quinazolinones
IN Allen, Eric E., Somerset, NJ, United States
Olson, Richard E., Wilmington, DE, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
E. I. Du Pont de Nemours and Co., Wilmington, DE, United States (U.S. corporation)
PI US 5308846 19940503 <--
AI US 1993-96125 19930722 (8)
RLI Continuation of Ser. No. US 1992-923273, filed on 31 Jul 1992, now patented, Pat. No. US 5256667 which is a continuation-in-part of Ser. No. US 1991-765626, filed on 25 Sep 1991, now patented, Pat. No. US 5202322
DT Utility
FS Granted
LN.CNT 1616
INCL INCLM: 514/259.000
INCLS: 514/228.200; 514/234.500; 514/255.000; 514/260.000; 544/057.000; 544/058.600; 544/116.000; 544/243.000; 544/284.000; 544/285.000; 544/287.000
NCL NCLM: 514/252.170
NCLS: 514/228.200; 514/234.500; 544/057.000; 544/058.600; 544/116.000; 544/243.000; 544/284.000; 544/285.000; 544/287.000

IC [5]
ICM: A61K031-505
ICS: C07D413-12; C07D487-04; C07D471-04
EXF 514/228.2; 514/234.5; 514/255; 514/259; 514/260; 544/57; 544/58.6; 544/116; 544/284; 544/285; 544/287; 544/243
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 17 OF 21 USPATFULL
AN 93:89674 USPATFULL
TI Quinazolinones and pyridopyrimidinones
IN Allen, Eric E., Somerset, NJ, United States
Olson, Richard E., Wilmington, DE, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
E. I. Du Pont De Nemours & Co., Willmington, DE, United States (U.S. corporation)
PI US 5256667 19931026 <--
AI US 1992-923273 19920731 (7)
RLI Continuation-in-part of Ser. No. US 1991-765626, filed on 25 Sep 1991, now patented, Pat. No. US 5202322
DT Utility
FS Granted
LN.CNT 1575
INCL INCLM: 514/259.000
INCLS: 514/243.000; 514/258.000; 514/260.000; 544/111.000; 544/112.000; 544/114.000; 544/120.000; 544/122.000; 544/184.000; 544/244.000; 544/256.000; 544/279.000
NCL NCLM: 514/252.160
NCLS: 514/217.060; 514/243.000; 514/264.100; 544/111.000; 544/112.000; 544/114.000; 544/120.000; 544/122.000; 544/184.000; 544/244.000; 544/256.000; 544/279.000
IC [5]
ICM: A61K031-505
ICS: C07D413-12; C07D487-04; C07D471-04
EXF 544/244; 544/279; 544/283; 544/284; 544/285; 544/287; 544/289; 544/290; 544/292; 544/184; 544/256; 544/111; 544/112; 544/114; 544/120; 544/121; 544/122; 514/259; 514/260
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 18 OF 21 USPATFULL
AN 93:52582 USPATFULL
TI Xanthine compounds and compositions, and methods of using them
IN Noverola, Armando V., Barcelona, Spain
Soto, Jose M. P., Barcelona, Spain
Mauri, Jacinto M., Barcelona, Spain
Gristwood, Robert W., Barcelona, Spain
PA Laboratorios Almirall SA, Barcelona, Spain (non-U.S. corporation)
PI US 5223504 19930629 <--
WO 9109859 19910711 <--
AI US 1991-743388 19910816 (7)
WO 1990-GB2027 19901227
19910816 PCT 371 date
19910816 PCT 102(e) date
PRAI GB 1989-29208 19891227
DT Utility
FS Granted
LN.CNT 428
INCL INCLM: 514/263.000
INCLS: 544/267.000; 544/273.000
NCL NCLM: 514/263.240
NCLS: 514/263.340; 544/267.000; 544/273.000

IC [5]
ICM: C07D473-08
ICS: A61K031-52
EXF 544/273; 544/262; 544/266; 544/267; 514/263
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 19 OF 21 USPATFULL
AN 93:29200 USPATFULL
TI Quinazolinone and pyridopyrimidine a-II antagonists
IN Allen, Eric E., Edison, NJ, United States
Olson, Richard E., Wilmington, DE, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
E. I. du Pont de Nemours and Company, Wilmington, DE, United States (U.S. corporation)
PI US 5202322 19930413 <--
AI US 1991-765626 19910925 (7)
DT Utility
FS Granted
LN.CNT 1450
INCL INCLM: 514/228.200
INCLS: 514/234.200; 514/234.500; 514/228.500; 514/255.000; 514/259.000; 514/260.000; 544/284.000; 544/285.000; 544/287.000; 544/116.000; 544/117.000; 544/057.000; 544/058.600
NCL NCLM: 514/228.200
NCLS: 514/080.000; 514/081.000; 514/228.500; 514/234.200; 514/234.500; 514/252.020; 514/252.170; 514/266.200; 514/266.230; 544/057.000; 544/058.600; 544/116.000; 544/117.000; 544/284.000; 544/285.000; 544/287.000
IC [5]
ICM: A61K031-54
ICS: A61K031-505; C07D239-90; C07D239-96
EXF 544/284; 544/285; 544/58.6; 544/57; 544/116; 544/287; 514/255; 514/259; 514/260; 514/234.5; 514/228.2
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 20 OF 21 USPATFULL
AN 93:1386 USPATFULL
TI Dihydro-isoquinoline derivatives, processes for their production, pharmaceutical compositions containing them, and their use in treating asthma
IN Naef, Reto, Rheinfelden, Switzerland
PA Sandoz Ltd., Basel, Switzerland (non-U.S. corporation)
PI US 5177085 19930105 <--
AI US 1991-805662 19911212 (7)
PRAI GB 1990-27055 19901213
DT Utility
FS Granted
LN.CNT 579
INCL INCLM: 514/307.000
INCLS: 546/144.000
NCL NCLM: 514/307.000
NCLS: 546/144.000
IC [5]
ICM: A61N031-47
ICS: C07D217-16
EXF 546/144; 514/307
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 21 OF 21 USPATFULL
AN 92:106826 USPATFULL

TI Angiotensin II antagonists incorporating a substituted indole or dihydroindole
IN Bagley, Scott, Rahway, NJ, United States
Greenlee, William J., Teaneck, NJ, United States
Dhanoa, Daljit S., Tinton Falls, NJ, United States
Patchett, Arthur A., Westfield, NJ, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 5175164 19921229 <--
AI US 1991-710413 19910605 (7)
DT Utility
FS Granted
LN.CNT 3271
INCL INCLM: 514/259.000
INCLS: 544/244.000; 544/279.000; 544/284.000; 544/287.000
NCL NCLM: 514/264.100
NCLS: 514/081.000; 514/266.200; 544/244.000; 544/279.000; 544/284.000; 544/287.000
IC [5]
ICM: A61K031-505
ICS: C07D471-14; C07D239-72
EXF 544/279; 544/284; 544/287; 544/244; 514/259
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d 1-21 kwic ab

L7 ANSWER 1 OF 21 USPATFULL
TI Methods for treating an ischemic disorder and improving **stroke** outcome
PI US 6316403 B1 20011113
WO 9813058 19980402
SUMM . . . mice has led to a burgeoning number of reports describing the effects of specific gene products on the pathophysiology of **stroke**. Although focal cerebral ischemia models in rats have been well-described, descriptions of a murine model of middle cerebral artery occlusion. . .
SUMM . . . deleterious effects in the early reperfusion period, but the mechanisms and effects of neutrophil influx in the pathogenesis of evolving **stroke** remains controversial.
DRWD FIGS. 2A, 2B, 2C and 2D. Effect of preoperative neutrophil depletion on indices of **stroke** outcome. C57B1/J6 male mice were subjected to transient middle cerebral artery occlusion as described above (Wild Type, n=16), and compared. . .
DRWD FIGS. 7A, 7B, 7C and 7D. Role of ICAM-1 in **stroke** outcome. Transient middle cerebral artery occlusion was performed as described in
ICAM-1 +/+ (Wild Type, n=16) or ICAM-1 -/- (n=13) mice, and indices of **stroke** outcome measured as described in FIG. 2. FIG. 7A. Effect of ICAM-1 on infarct volume, FIG. 7B. neurologic deficit score,. . .

DRWD FIGS. 14A, 14B and 14C. Effects of mouse strain on **stroke** outcome. Mice (20-23 gm males) were subjected to 45 minutes of MCA occlusion (using 12 mm 6.0 occluding suture) followed by 24 hours of reperfusion, and indices of **stroke** outcome determined. FIG. 14A. Effects of strain on infarct volume, determined as a percentage of ipsilateral hemispheric volume, as described. . .
DRWD FIGS. 15A, 15B and 15C. Effects of animal size and diameter of the occluding suture on **stroke** outcome. Male CD-1 mice of the indicated sizes were subjected to middle cerebral artery occlusion (45 minutes) followed by reperfusion. . .

DRWD FIGS. 16A, 16B and 16C. Effects of temperature on **stroke** outcome. Male C57/B16 mice were subjected to 45 minutes of MCA occlusion (6.0 suture) followed by reperfusion. Core temperatures were. . . cages with ambient temperature maintained at 37.degree. C. for the duration of observation. Twenty-four hours following MCA occlusion, indices of **stroke** outcome were recorded; FIG. 16A. infarct volume, FIG. 16B. neurological deficit score, and FIG. 16C. cerebral blood flow, measured as. . .

DRWD . . . suture in 22 gram Male C57/B16 mice, as described in the Methods section. Twenty-four hours following MCA occlusion, indices of **stroke** outcome were recorded; FIG. 17A. infarct volume, FIG. 17B. neurological deficit score, and FIG. 17C. cerebral blood flow, measured as. . .

DRWD FIGS. 21A, 21B and 21C. Effect of the P-selectin gene on **stroke** outcomes. Middle cerebral artery occlusion was performed for 45 minutes, followed by 22 hours of reperfusion in P-selectin +/+ (n=10). . .

DRWD FIGS. 22A, 22B, 22C and 22D. Effect of P-selectin blockade on **stroke** outcomes. PS +/+ mice were given either a blocking rat anti-mouse anti-P-selectin IgG (clone RB 40.34, 30 .mu.g/mouse) or a. . .

DRWD . . . expressed as the percent of infarction of the ipsilateral hemisphere. These data show that inhaled CO reduces infarct volumes following **stroke**.

DRWD FIG. 23B. The effect of carbon monoxide inhalation on mortality following **stroke**. Experiments were performed as described above. Mortality at 4 hours is shown. These data show that inhaled CO reduces mortality following **stroke**.

DRWD FIGS. 24A, 24B, and 24C. FIG. 24A. Dose-response of inhaled carbon monoxide on **stroke** outcome. Experiments are described above. CO was inhaled at the indicated doses. These data show that inhaled CO reduces infarct. . . fashion, with 0.1% providing optimal protection.

FIGS. 24B and 24C. Role of heme oxygenase, the enzyme which makes CO, in **stroke**. Animals were given either vehicle (DMSO) alone as a control or zinc protoporphyrin IX (ZnPP) or tin protoporphyrin IX (SnPP).. . . oxygenase. Left panel shows infarction volumes. Right panel shows mortality. These experiments demonstrate that when heme oxygenase activity is blocked, **stroke** outcomes are worse (larger infarcts and higher mortalities). Because biliverdin administration is not protective, these data suggest that the other. . .

DRWD . . . of focal cerebral ischemia on heme oxygenase I (HO-I) induction. FIGS. 26A-26C show in situ hybridization of HO-I mRNA in **stroke** (FIG. 26B) and in controls (FIGS. 26A and 26C). FIGS. 26D-26F show immunohistochemistry of HO-I protein. FIG. 26E shows that the protein is expressed in blood vessels and astrocytes following **stroke**. FIGS. 26D and 26F show that the protein is not expressed in blood vessels and astrocytes in controls.

DRWD . . . oxygenase I (HO-I) mRNA induction. Contralateral indicates the nonstroke side of the brain. Ipsilateral indicates the brain side subjected to **stroke**. In both animals, the side of the brain subjected to **stroke** demonstrates increased HO-I but the nonstroke side does not.

DRWD . . . also confer protection against subsequent ischemic events, which was found to be true in mice subjected to hypoxia followed by **stroke**.

DRWD FIGS. 33A-33B. Effect of the P-selectin gene on **stroke** outcomes. Middle cerebral artery occlusion was performed for 45 minutes, followed by 22 hours of reperfusion in P-selectin +/+ (n=10). . .

DRWD FIG. 34. Effect of P-selectin blockade on **stroke** outcomes. PS +/+ mice were given either a blocking rat anti-mouse anti-P-selectin IgG (clone RB 40.34, 30 .mu.g/mouse) or a. . .

DRWD . . . solution) by dorsal penile vein injection (Collagenase+rt-PA). **p<0.001 vs. Sham or Control. FIG. 36B. Effect of rt-PA following focal ischemic **stroke** on murine quantitative ICH. Mice were subjected to 45 minutes of MCA occlusion followed by reperfusion and then 1) intravenous 0.2 .mu.l of normal saline solution (**Stroke**+Saline) or 2) intravenous tissue plasminogen activator (15 mg/kg in 0.2 .mu.l normal saline solution) (**Stroke**+rt-PA). Brains were harvested 24 h later and the spectrophotometric hemoglobin assay was performed to quantify ICH. **p<0.05.

DRWD FIG. 37. Demonstration of the scoring system used for the visual determination of ICH following **stroke**. Each slice, taken from different animals subjected to **stroke**, represents the coronal slice of brain which exhibits the maximal hemorrhagic diameter. The numbers correspond to the visually determined hemorrhage. . .

DRWD . . . in the Methods section. *p<0.05 vs. Collagenase, p<0.005 vs. Sham or Control. FIG. 38B. Effect of rt-PA following focal ischemic **stroke** on murine visual ICH score. Mice were subjected to 45 minutes of MCA occlusion followed by reperfusion and then 1) intravenous 0.2 .mu.l of normal saline solution (**Stroke**+Saline) or 2) intravenous tissue plasminogen activator (15 mg/kg in 0.2 .mu.l normal saline solution) (**Stroke**+rt-PA). Brains were harvested 24 h later, sectioned into 1 mm coronal slices, and scored by a blinded observer as described. . .

DRWD FIGS. 40A-40F. FIG. 40A. Effect of **stroke** and Factor IXai administration in **stroke** on the accumulation of radiolabeled platelets. .sup.111 Indium-platelets were administered either in control animals without **stroke** (n=4), or in animals immediately prior to **stroke** with (n=7) or without preoperative administration of Factor IXai (300 .mu.g/kg, n=7). Platelet accumulation is expressed as the ipsilateral cpm/contralateral cpm. Means.+-.SEM are shown. *p<0.05 vs No **Stroke**; **p<0.05 vs **Stroke**+Vehicle. FIG. 40B. Accumulation of fibrin in infarcted cerebral tissue. Twenty-two hours following focal cerebral ischemia and reperfusion, a brain was. . . neoepitope expressed on the gamma--gamma chain dimer of crosslinked fibrin. FIG. 40C-40F. Immunohistochemical identification of sites of fibrin formation in **stroke**. Using the same antibody as described in FIG. 2b to detect fibrin, brains were harvested from two mice following **stroke** (upper and lower panels each represent a mouse). Arrows identify cerebral microvessels. Note that in both ipsilateral hemispheres (right panels),. . .

DRWD FIGS. 41A-41C. FIG. 41A. Effect of Factor IXai on relative CBF in a murine **stroke** model, measured by laser doppler. CBF in Factor IXai-treated animals (300 .mu.g/kg, n=48, dashed line) is significantly higher at 24. . . than vehicle-treated controls (n=62). Means.+-.SEM are shown. *p<0.05. FIG. 41B. Effect of Factor IXai on infarct volumes in a murine **stroke** model, measured by TTC-staining of serial coronal sections. Animals were given vehicle (n=62) or Factor IXai (300 .mu.g/kg, n=48). Means.+-.SEM are shown. *p<0.05. FIG. 41C.

Dose-response of Factor IXai in **stroke**. Factor IXai was administered immediately prior to the onset of **stroke**, and cerebral infarct volumes determined as described in FIG. 41B above. N=62, 48, 6, and 6, for Vehicle, 300 .mu.g/kg,. . .

DRWD FIG. 43. Effect of timing of Factor IXai administration on cerebral infarct volumes when given after the onset of **stroke**. Mice were subjected to focal cerebral ischemia and reperfusion as described in the Methods section. The preocclusion administration (leftmost 2 bars) data is that shown FIG. 42B. In additional experiments to determine the effects of Factor IXai administered after **stroke**, immediately following withdrawal of the intraluminal occluding suture, vehicle (normal saline, n=13) or Factor IXai (300 .mu.g/kg, n=7) was administered. . .

DETD . . . such as nitroglycerin or nitroprusside, a cyclic nucleotide analog such as a cyclic GMP or cyclic AMP analog, or a **phosphodiesterase inhibitor**.

DETD . . . embolus, a myocardial infarction, a transient ischemic attack, unstable angina, a reversible ischemic neurological deficit, sickle cell anemia or a **stroke** disorder.

DETD . . . lung ischemia, unstable angina, a reversible ischemic neurological deficit, adjunct thromolytic activity, excessive clotting conditions, sickle cell anemia or a **stroke** disorder.

DETD . . . improving an ischemic disorder in a subject which includes: a) administering the compound to an animal, which animal is a **stroke** animal model; b) measuring **stroke** outcome in the animal, and c) comparing the **stroke** outcome in step (b) with that of the **stroke** animal model in the absence of the compound so as to identify a compound capable of improving an ischemic disorder in a subject. The **stroke** animal model includes a murine model of focal cerebral ischemia and reperfusion. The **stroke** outcome may be measured by physical examination, magnetic resonance imaging, laser doppler flowmetry, triphenyl tetrazolium chloride staining, chemical assessment of neurological deficit, computed tomography scan, or cerebral cortical blood flow. The **stroke** outcome in a human may be measured also by clinical measurements, quality of life scores and neuropsychometric testing. The compound. . .

DETD . . . accumulation of white blood cells in a subject which includes:a) administering the compound to an animal, which animal is a **stroke** animal model; b) measuring **stroke** outcome in the animal, and c) comparing the **stroke** outcome in step (b) with that of the **stroke** animal model in the absence of the compound so as to identify a compound capable of preventing the accumulation of. . .

DETD . . . the surface of the vessels in the subject may also be a target for treatment. In a mouse model of **stroke**, administration of TPA as a thrombolytic agent caused some visible hemorrhaging along with improvement of the **stroke** disorder. However, administration of a P-selectin antagonist also improved **stroke** disorder in the animal model, but without the coincident hemorrhaging. The present invention may be used in conjunction with a. . .

DETD This invention also provides for pharmaceutical compositions including therapeutically effective amounts of protein compositions and compounds capable of treating **stroke** disorder or improving **stroke** outcome in the subject of the invention together with suitable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers useful in treatment. . . of compositions will depend

on the physical and chemical properties of the compound capable of alleviating the symptoms of the **stroke** disorder or improving the **stroke** outcome in the subject.

DETD . . . the risk of triggering a severe immune response. The compound of the present invention capable of alleviating symptoms of a **cognitive** disorder of memory or learning may be delivered in a microencapsulation device so as to reduce or prevent an host. . .

DETD The present invention provides for a pharmaceutical composition which comprises an agent capable of treating a **stroke** disorder or improving **stroke** outcome and a pharmaceutically acceptable carrier. The carrier may include but is not limited to a diluent, an aerosol, a. . .

DETD Cerebral Protection in Homozygous Null ICAM-1 Mice Following Middle Cerebral Artery Occlusion: Role of Neutrophil Adhesion in the Pathogenesis of **Stroke**

DETD To investigate whether polymorphonuclear leukocytes (PMNs) contribute to adverse neurologic sequelae and mortality following **stroke**, and to study the potential role of the leukocyte adhesion molecule Intercellular Adhesion Molecule-1 (ICAM-1) in the pathogenesis of **stroke**, a murine model of transient focal cerebral ischemia was employed consisting of intraluminal middle cerebral artery (MCA) occlusion for 45. . . in the ipsilateral hemisphere, with immunohistochemistry localizing increased ICAM-1 expression on cerebral microvascular endothelium. The role of ICAM-1 expression in **stroke** was investigated in homozygous null ICAM-1 mice (ICAM-1 -/-) in comparison with wild type controls (ICAM-1 +/+). ICAM-1 -/- mice. . .

DETD . . . relevance of adhesion molecule expression in the brain remains controversial, however; data from a trial of monoclonal anti-ICAM-1 antibody in **stroke** in humans is not yet available. In animal models, there is conflicting experimental evidence regarding the effectiveness of anti-adhesion molecule strategies in the treatment of experimental **stroke**.sup.21-23. To determine whether ICAM-1 participates in the pathogenesis of postischemic cerebral injury, the experiments reported here were undertaken in a. . . to cerebral infarction following ischemia and reperfusion, providing strong evidence for an exacerbating role of ICAM-1 in the pathophysiology of **stroke**.

DETD . . . and is based upon similar scoring systems used in rats.sup.28,29 which are based upon the contralateral movement of animals with **stroke**; following cerebral infarction, the contralateral side is "weak" and so the animal tends to turn towards the weakened side. Previous. . .

DETD Neutrophil Accumulation in **Stroke**

DETD Effect of Neutrophil Depletion on **Stroke** Outcome

DETD To determine the effect of neutrophil influx on indices of **stroke** outcome, mice were immunodepleted of neutrophils beginning three days prior to surgery. When surgery was performed on the fourth day,. . . peripheral blood. Neutropenic mice (n=18) were subjected to 45 min cerebral ischemia and 22 hours of reperfusion, and indices of **stroke** outcome determined. Infarct volumes were 3-fold smaller in neutropenic animals compared with wild type controls (11.1.+-.1.6% vs 33.3.+-.6.4%, p<0.001; FIG.. . .

DETD ICAM-1 Expression in Murine **Stroke**

DETD Role of ICAM-1 in **Stroke**

DETD To explore the role of ICAM-1 in **stroke**, transgenic mice which

were homozygous ICAM-1 deficient.sup.24 were studied in the murine model of focal cerebral ischemia and reperfusion. Because variations in cerebrovascular anatomy have been reported to result in differences in susceptibility to experimental **stroke** in mice.sup.37, India ink staining was performed on the Circle of Willis in homozygous null (ICAM-1 -/-) and ICAM-1 +/+. . .

DETD Experiments were the performed to investigate whether expression of ICAM-1 has a pathophysiologic role in outcome following **stroke** . ICAM-1 -/- mice (n=13) were significantly protected from the effects of focal cerebral ischemia and reperfusion, based on a 3.7-fold. . .

DETD Epidemiologic evidence in humans suggests that neutrophils contribute to both the initiation of **stroke**.sup.38 as well as to cerebral tissue injury and poor clinical outcome.sup.39, with a potential role for neutrophils in postischemic hypoperfusion,. . . neuronal dysfunctions, and scar formation.sup.40-44. Although there is considerable experimental evidence which suggests that neutrophils can exacerbate tissue damage following **stroke**.sup.13,45-48, certain pieces of experimental data have stoked controversy by failing to find an association between agents which block neutrophil accumulation and indices of **stroke** outcome. In a rat model of **stroke**, antibody-mediated depletion of neutrophils prior to **stroke** significantly decreased brain water content and infarct size.sup.13. However, cyclophosphamide-induced leukocytopenia in a gerbil model.sup.49 or anti-neutrophil antibody administration to. . .

DETD . . . the post-ischemic period.sup.15,16,36,45. Not only do neutrophils accumulate during the post-ischemic period in mice, but their presence exacerbates indices of **stroke** outcome. When animals were made neutropenic prior to the ischemic event, cerebral infarcts were smaller, with improved cerebral perfusion following the ischemic event. These data are quite similar to that reported in a rabbit model of thromboembolic **stroke**, in which immunodepletion of neutrophils resulted both in reduced infarction volume and improved blood flow.sup.35. Because neutrophils contribute to murine post-ischemic cerebral injury, a strategy was pursued to elucidate the role of ICAM-1 in the pathophysiology of **stroke** using deletionally mutant ICAM-1 mice.sup.24. Experiments indicate that homozygous null ICAM-1 mice are relatively resistant to the deleterious effects of. . .

DETD To demonstrate the role of both neutrophils and ICAM-1 in the pathogenesis of tissue injury in **stroke**, the studies reported here used several methods for assessing **stroke** outcome. Although numerous investigators have used TTC staining to quantify cerebral infarct volumes.sup.36,30-32,37,53, there has been some controversy as to. . . these limitations, however, the studies reported here incorporate three additional methods to define the role of neutrophils and ICAM-1 in **stroke** outcome, including neurologic deficit score, relative cerebral blood flow to the affected area, and mortality. These additional measures, which do. . . the accuracy of TTC staining, contribute strongly to the identification of a pathogenic role for both neutrophils and ICAM-1 in **stroke**.

DETD . . . Although P-selectin-dependent neutrophil recruitment appears to be deleterious following cardiac ischemia and reperfusion.sup.57, its pathophysiologic relevance in the setting of **stroke** has not

yet been determined. While hypoxia induces de novo synthesis of the bioactive lipid platelet activating factor (PAF).sup.11, in. . .

DETD Understanding the role of ICAM-1 in the pathophysiology of **stroke** appears to be of particular relevance in humans for several reasons. Increased cerebrovascular ICAM-1 expression has been demonstrated in primates. . . hours in these models suggests that ICAM-1 mediated neutrophil-endothelial interactions may be targeted in future pharmacologic strategies to improve human **stroke** outcome, as this time frame represents a realistic clinical window for therapeutic intervention.

DETD . . . and reduced mortality. These data suggest that pharmacologic strategies targeted at interfering with neutrophil-endothelial interactions may improve the outcome following **stroke** in humans.

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effects of neutrophil depletion. **Stroke** 25: 1469-75.

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a focal cerebral ischemia model in rats. **Stroke** 24:117-121.

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platelets in a rabbit model of thromboembolic **stroke**. **Stroke**. 22(1):44-50.

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DETD . . . Rusche. 1994. Postischemic administration of an anti-Mac-1 antibody reduces ischemic cell damage after transient middle cerebral artery occlusion in rats. **Strokes** 25: 869-76.

DETD 59. Sornas R., H. Ostlund, and R. Muller. 1972. Cerebrospinal fluid cytology after **stroke**. Arch Neurol 26: 489-501.

DETD . . . mice has led to a burgeoning number of reports describing the effects of specific gene products on the pathophysiology of **stroke**. Although focal cerebral ischemia models in rats have been well-described, descriptions of a murine model of middle cerebral artery occlusion. . . remain undefined. It was hypothesized that slight technical modifications would result in widely discrepant results in a murine model of **stroke**, and that controlling surgical and procedural conditions could lead to reproducible physiologic and anatomic **stroke** outcomes. To test this hypotheses, a murine model was established which would permit either permanent or transient focal cerebral ischemia. . . size of the suture which obstructs the vascular lumen. When these variables were kept constant, there was remarkable uniformity of **stroke** outcome. These data emphasize the protective effects of hypothermia in **stroke**, and should help to standardize techniques among different laboratories to provide a cohesive framework for evaluating the results of future. . .

DETD . . . of genetically altered mice provides a unique opportunity to evaluate the role of single gene products in the pathophysiology of **stroke**. Although there is an increasing number of reports about the effect of cerebral ischemia in transgenic mice, to date, there. . . description of the murine models involved, nor is there a detailed analysis of potentially important procedural variables which may effect **stroke** outcome. Most descriptions of a murine model (1,4,8,9,14,17-19,23,24) are devolved descriptions of the widely used rat models of focal cerebral. . . published studies. Because pilot data demonstrated that minor differences in operative procedures or postoperative care translated into major differences in **stroke** outcome, the current study was undertaken to systematically identify important surgical, technical, and anatomic considerations required to obtain consistent results. . .

DETD . . . based on modifications of the original rat model (26). This study identifies procedural variables that have a large impact on **stroke** outcome which have not been previously reported in

technical descriptions of murine stoke models. These variables include suture length and. . . in reperfused animals can be made to approximate those seen with permanent occlusion. Understanding potential
model-dependent sources of variability in **stroke** outcome can help to clarify divergent results between different laboratories. Adoption of a standardized model which yields consistent results is an important first step towards the use of transgenic mice in the study of the pathophysiology of **stroke**.

DETD Calculation of **Stroke** Volume

DETD . . . the need for arterial puncture and abdominal manipulation to measure these physiologic parameters, animals were designated solely for
these measurements (**stroke** volumes, neurologic outcome, and cerebral blood flows were not measured in these same animals).

DETD **Stroke** volumes, neurologic outcome scores, cerebral blood flows and arterial blood gas data were compared using an unpaired Student's t-test. Values. . .

DETD Three different commonly used mouse strains (CD1, C57/B16, and 129J) were used to compare the variability in **stroke** outcome following permanent focal cerebral ischemia. To establish that there were no gross anatomic differences in collateralization of the cerebral.
. .

DETD To investigate the effects of mouse size on **stroke** outcome, mice of two different sizes (23+0.4 g and 31+0.7 g) were subjected to permanent focal cerebral ischemia. To eliminate. . .

DETD To establish the role of perioperative hypothermia on the **stroke** volumes and neurologic outcomes following MCA occlusion, small C57/B16 mice (22+0.4 g) were subjected to permanent MCA occlusion with 12. .
.

DETD . . . to an increasing use of murine models of focal cerebral ischemia to impute specific gene products in the pathogenesis of **stroke**. Although recent publications describe the use of an intraluminal suture to occlude the middle cerebral artery to create permanent and/or. . .

DETD . . . three strains tested, 129J mice are particularly resistant to neurologic injury following MCA occlusion. Although Barone similarly found differences in **stroke** volumes between 3 strains of mice (BDF, CRW and BALB/C), these differences were ascribed to variations in the posterior communicating. . .

DETD As **stroke** outcome differs significantly between 2 strains of mice (129J and C57/B16) commonly used to produce transgenic mice via homologous recombination. . .

DETD . . . experiments using larger bore occluding suture in larger animals suggest that the increased propensity of smaller animals to have
larger **strokes** was not due to a relative resistance of larger animals to ischemic neuronal damage, but was rather due to small. . .

DETD . . . period, and that temperature differences up to 90 minutes following MCA occlusion can have a profound effect on indices of **stroke** outcome following MCA occlusion (longer durations of normothermia were not studied). While others have ensured normothermia using a feedback system. . . as the durations involved, so that experimental results can be compared both within and between Centers studying the pathophysiology of **stroke**.

DETD . . . tested (45 minutes of ischemia followed by 23 hours of reperfusion), no significant differences were found in any index of **stroke** outcome. Variable durations of ischemia and reperfusion have been reported in other murine models of transient cerebral

ischemia, with ischemic. . . reperfusion led to massive infarction and nearly 100% mortality within 4-6 hours in normothermic animals (unpublished observation). Although indices of **stroke** outcome may be measured earlier than 24 hours, the 24 hour observation time was elected because observation at this time permits the study of delayed penumbral death, which is likely to be clinically relevant to the pathophysiology of **stroke** in humans. Furthermore, 24 hours has been shown in a rat model to be sufficient for full infarct maturation (3,12,15,16)

DETD . . . between different laboratories. In addition, these studies provide a framework for understanding important procedural variables which can greatly impact on **stroke** outcome, which should lead to a clear understanding of non-procedure related differences under investigation. Most importantly, this study points to. . . strain, animal and suture size, and temperature in experimental as well as control animals. Conditions can be established so that **stroke** outcome is similar between models of permanent focal cerebral ischemia and transient focal cerebral ischemia, which should facilitate direct comparison. . . future studies in transgenic animals, to facilitate an understanding of the contribution of specific gene products in the pathophysiology of **stroke**.

DETD . . . carotid dissection; Sham, anesthetized animals undergoing the surgical described in the text, immediately prior to introduction of the

occluding suture; **Stroke**, anesthetized animals undergoing the surgical described in the text, immediately after introduction of the occluding suture. p=NS for all between-group. . .

DETD

PARAMETER	PREOPERATIVE	SHAM	**STROKE**
MAP	102 .+-. 5.5	94 .+-. 1.9	88 .+-. 4.9
pH	7.27 .+-. 0.02	7.23 .+-. 0.04	7.28 .+-. 0.01
pCO.sub.2	46 .+-..	.	.

DETD . . . Bartkowski H M: Evaluation of 2,3,5-triphenyltetrazolium chloride as a stain for detection and quantification of experimental cerebral infarction in rats. **Stroke** 17:1304-1308, 1986.

DETD . . . Pitts L H, Tsuji M: Rat middle cerebral artery occlusion: evaluation of the model and development of a neurologic examination. **Stroke** 17:472-476, 1986.

DETD Buchan A M, Xue D, Slivka A: A new model of temporary focal neocortical ischemia in the rat. **Stroke** 23:273-279, 1992.

DETD . . . Kaplan B, Jacewicz M, Pulsinelli W: Vontinuous measurement of cerebral cortical blood flow by laser doppler flowmetry in a rat **stroke** model. J Cereb Blood Flow Metab 9:589-596, 1989.

DETD Ginsberg M D, Busto R: Rodent models of cerebral ischemia. **Stroke** 20:1627-1642, 1989.

DETD Kader A, Frazzini V I, Solomon R A, Trifiletti R R: Nitric oxide production during focal cerebral ischemia in rats. **Stroke** 24:1709-1716, 1993.

DETD Memezawa H, Smith M L, Siesjo B K: Penumbral tissues salvaged by reperfusion following middle cerebral artery occlusion in rats. **Stroke** 23:552-559, 1992.

DETD . . . C J, Kamii H: human copper-zinc superoxide dismutase transgenic

mice are highly resistant to reperfusion injury after focal cerebral ischemia. **Stroke** 25:165-170, 1994.

DETD Yang G-Y, Betz A L: Reperfusion-induced injury to the blood-brain barrier after middle cerebral artery occlusion in rats. **Stroke** 25:1658-65, 1994.

DETD Zea-Longa E., Weinstein P R, Carlson S, Cummin R W: Reversible middle cerebral artery occlusion without craniectomy in rat. **Stroke** 20:84-91, 1989.

DETD . . . Injury In Mice Which Express the P-Selectin Gene: Identication of P-selectin Blockade as a New Target for the Treatment of **Stroke**

DETD There is currently a stark therapeutic void for the treatment of evolving **stroke**. Although P-selectin is rapidly expressed by hypoxic endothelial cells in vitro, the functional significance of P-selectin expression in **stroke** remains unexplored. In order to identify the pathophysiological consequences of P-selectin expression and to identify P-selectin blockade as a potential new approach for the treatment of **stroke**, experiments were performed using a murine model of focal cerebral ischemia and reperfusion. Early P-selectin expression in the post-ischemic cerebral. . . blockade of P-selectin in PS +/+ mice using a monoclonal antibody directed against murine P-selectin also improved early reflow and **stroke** outcome compared with controls. These data are the first to demonstrate a pathophysiological role for P-selectin in **stroke**, and suggest that P-selectin blockade may represent a new therapeutic target for the treatment of **stroke**.

DETD Ischemic **stroke** constitutes the third leading cause of death in the United States today.sup.1. Until very recently, there has been no direct treatment to reduce cerebral tissue damage in evolving **stroke**. Although the NINDS .sup.2 and ECASS.sup.3 rt-PA acute **stroke** studies have suggested that there are potential therapeutic benefits of early reperfusion.sup.4, the increased mortality observed following streptokinase treatment of acute ischemic **stroke**.sup.5 highlights the sobering fact that there is at the present time no clearly effective treatment for evolving **stroke** . This void in the current medical armamentarium for the treatment of **stroke** has led to a number of innovative approaches.sup.6, yet other than rt-PA, none have reached the clinical realm. To identify a potential safe and efficacious treatment for evolving **stroke**, attention has been focussed on the deleterious role of recruited neutrophils. Recent work in a murine model of reperfused **stroke** has demonstrated that depletion of neutrophils (PMNs) prior to **stroke** minimizes cerebral tissue injury and improves functional outcome.sup.7 ; mice which lack the specific cell adhesion molecule, ICAM-1, are similarly. . . is an important early mediator of the neutrophil rolling.sup.9, which facilitates ICAM-1-mediated neutrophil arrest. Although P-selectin is expressed in primate **stroke** .sup.10, there are no published data which addresses the functional significance of P-selectin expression in any model of either reperfused or nonreperfused **stroke**.

DETD To explore the pathophysiological role of P-selectin in **stroke** , a murine model of focal cerebral ischemia and reperfusion.sup.11 was employed using both will type mice and mice which were. . . P-selectin expression following middle cerebral artery occlusion is associated with reduced cerebral reflow following reperfusion and a worse outcome following **stroke**, but that P-selectin blockade confers a significant degree of postischemic cerebral protection. These studies represent the first demonstration of the pathophysiological role of P-selectin expression in **stroke**, and suggest the exciting possibility that anti-P-selectin strategies may prove useful for the treatment of reperfused **stroke**.

DETD . . . This method of calculating infarct volumes has been used previously.sup.7,11,13,18, and has been correlated with the other functional indices of **stroke** outcome which are described

above.
DETD P-selectin Expression in Murine **Stroke**
DETD . . . of leukocyte adhesion to activated endothelial cells .sup.21, early cerebral P-selectin expression was examined in a murine model of reperfused **stroke**. Mice given a .sup.125 I-labelled rat monoclonal anti-murine P-selectin IgG prior to surgery demonstrated a 216% increase in accumulation of. . .
DETD neutrophil Accumulation in Murine **Stroke**
DETD To delineate the time course over which PMN influx occurs following **stroke**, .sup.111 In-labeled PMN accumulation was measured in wild type (PS +/+) mice prior to MCAO, immediately following and 10 minutes. . .
DETD Because variations in cerebrovascular anatomy have been reported to result in differences in susceptibility to experimental **stroke** in mice .sup.24, India ink/carbon black staining was performed to visualize the the vascular pattern of the Circle of Willis. . .
DETD **Stroke** Outcome
DETD The functional significance of P-selectin expression was tested by comparing indices of **stroke** outcome in PS -/- mice to those in PS +/+ controls. PS -/- mice were significantly protected from the effects. . .
DETD After having observed the functional role of P-selectin expression in **stroke** using deletionally mutant mice, experiments were performed to determine whether pharmacological blockade of P-selectin could improve **stroke** outcome in PS +/+ mice. Using a strategy of administering a monoclonal rat anti-mouse P-selectin blocking antibody (clone RB 40.34,. . .
DETD Despite substantial progress in recent years in the primary prevention of **stroke** .sup.1, therapeutic options to treat evolving **stroke** remain extremely limited .sup.6. Although the publication of two landmark trials last fall demonstrating reduced morbidity following treatment of ischemic **stroke** with rt-PA.sup.2,3 was thought to usher in a new ear of thrombolytic therapy in the treatment of **stroke** .sup.4, enthusiasm has been tempered somewhat by the hemorrhagic transformation and increased mortality noted in patients with ischemic **stroke** treated with streptokinase .sup.5. These divergent trials make it more critical than ever that new safe therapies
be developed to treat evolving **stroke**. Although restoration of blood flow to postischemic brain affords new opportunities for early therapeutic intervention, reperfusion is a double-edged sword.. . . is not surprising that neutrophil influx into postischemic brain tissue can lead to further damage and worsen outcome following experimental **stroke**.sup.7,26-29. Using a murine model of focal cerebral ischemia and reperfusion, an important contributory role for the cell adhesion molecule ICAM-1 in neutrophil accumulation at 22 hours following **stroke** was recently identified .sup.7. However, augmented cerebrovascular endothelial ICAM-1 expression required de novo
transcriptional and translational events, which requires time.. . . storage pools to be rapidly expressed at the ischemic endothelial cell surface.sup.8,30. As the clinical trials of thrombolytic therapy for **stroke** demonstrate a narrow time window for potential benefit (within the first several hours of **stroke** onset) .sup.2,3,5, this suggests that strategies designed to interfere with the earliest phases of PMN adhesion might be of theoretical benefit in human **stroke**. These trials should result in greater numbers of patients presenting for earlier therapeutic intervention, increasing the
need to address the. . . In addition, these trials underscore the

pressing need to understand the contributions of individual adhesion molecules to the pathogenesis of **stroke**.

DETD . . . of P-selectin in other models of ischemia and reperfusion .sup.8,31-34, surprisingly little is known about the role of P-selectin in **stroke**. Knowledge of the specific role of P-selectin in the cerebral vasculature is important because adhesion molecule requirements vary between vascular. . .

DETD The only published study dealing with P-selectin in the ischemic brain is a histopathological description of primate **stroke**, in which P-selectin expression was increased in the lenticulostriate microvasculature .sup.10. Furthermore, there is no data which addresses the functional. . . study whether P-selectin expression contributes to post-ischemic cerebral neutrophil accumulation, no-reflow, and tissue injury in a murine model of reperfused **stroke**. Using a recently established model of focal cerebral ischemia and reperfusion in mice .sup.11, P-selectin expression was demonstrated by increased. . . is augmented in the reperfused tissue. This data in the murine model parallels that reported in a baboon model of **stroke** .sup.10, in which P-selectin expression was increased within 1 hour following the ischemic event.

DETD . . . with controls. When these data are considered along with previously published data demonstrating a deleterious role for ICAM-1 expression in **stroke** .sup.7, it becomes increasingly apparent that there are multiple means for recruiting PMNs to post-ischemic cerebral cortex, and that blockade of each represents a potential strategy to improve **stroke** outcome in humans. Given the current recognition of the importance of timely reperfusion in halting the advancing wavefront of neuronal death following **stroke**, interfering with PMN adhesion at its earliest stages appears to be an attractive option for reducing morbidity and mortality. In. . . opportunity for thrombolytic intervention .sup.42. The current set of studies contributes to the understanding of pathophysiological mechanisms operative in reperfused **stroke**. These studies suggest the need for clinical trials of therapies for evolving **stroke** which optimize the reperfusion milieu to reduce PMN accumulation.

DETD 1. Bronner L L, Kanter D S, Manson J E: Primary prevention of **stroke**. N Engl J Med 1995; 333(21):1392-1400

DETD 2. The National Institute of Neurological Disorders and **Stroke** rt-PA **Stroke** Study Group: Tissue Plasminogen activator for acute ischemic **stroke**. N Engl J Med 1995;333:1582-1587

DETD . . . Mahagne M H, Hennerici M, for the ECASS Study Group: Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric **stroke**. J A M A 1995;274(13):1017-1025.

DETD 4. del Zoppo G J: Acute **stroke**--on the threshold of a therapy. N Engl J Med 1995;333(13):1632-1633

DETD 5. Hommel M, Cornu C, Boutitie F, Boissel J P, The MultiCenter Acute **Stroke** Trial--Europe Stucy Group: Thrombolytic therapy with streptokinase in acute ischemic **stroke**. N Engl J Med 1996;335:145-150

DETD 6. Baringa M: Finding new drugs to treat **stroke**. Science 1996;272:664-666

DETD . . . Cerebral protection in homozygous null ICAM-1 mice after middle cerebral artery occlusion: role of neutrophil adhesion in the

pathogenesis of **stroke**. J Clin Invest 1996;97:209-216

DETD . . . M, Thomas W S, del Zoppo G J: P-Selectin and intercellular adhesion molecule-1 expression after focal brain ischemia and reperfusion. **Stroke** 1994;25:202-211

DETD . . . Dirnagl U, Kaplan B, Jacewicz M, Bulsinelli W: Continuous measurement of cerebral blood flow by laser-doppler flowmetry in a rat **stroke** model. J Cereb Blood Flow Metab 1989;9:589-596

DETD . . . Pitts L H, Tsuji M: Rat middle cerebral artery occlusion: evaluation of the model and development of a neurologic examination. **Stroke** 1986;17:472-476

DETD . . . Bartkowski H M: Evaluation of 2,3,5-triphenyltetrazolium chloride as a stain for detection and quantification of experimental cerebral infarction in rats. **Stroke** 1986;17:1304-1308

DETD 23. Levy D E, Van Uitert R L, Pike C L: Delayed postischemic hypoperfusion: a potentially damaging consequence of **stroke**. Neurology 1979;29:1245-1252

DETD . . . T P, Contreras T J: Polymorphonuclear leukocyte accumulation in brain regions with low blood flow during the early postischemic period. **Stroke** 1986;17:246-253

DETD 27. Kochanek P M, Hallenbeck J M: Polymorphonuclear leukocytes and monocytes/macrophages in the pathogenesis of cerebral ischemia and **stroke**. **Stroke** 1992;23(9):1367-1379

DETD . . . Dutka A J, Kochanek P M, Hallenbeck J M: Influence of granulocytopenia on canine cerebral ischemia induced by air embolism. **Stroke** 1989;20:390-395

DETD . . . McAuliffe T, Lodge P A, Gross C E: The role of neutrophils and platelets in a rabbit model of thromboembolic **stroke**. **Stroke** 1991;22(1):44-50

DETD . . . D, Copeland B R, Arfors K E: Inhibition of polymorphonuclear leukocyte adherence suppresses no-reflow after focal cerebral ischemia in baboons. **Stroke** 1992;23:712-718

DETD . . . has been described in brain microvessels following middle cerebral artery occlusion in baboons, the consequences of endothelial P-selection expression in **stroke** have not been determined. To define the role of P-selectin in **stroke**, a murine model of focal cerebral ischemia and reperfusion consisting of intraluminal middle cerebral artery (MCA) occlusion for 45 minutes. . . may contribute to cerebral no-reflow. Taken together, these data implicate an important role for P-selectin expression in the pathophysiology of **stroke**, and suggest novel pharmacologic strategies to improve **stroke** outcome.

DETD Absence of the P-selectin Gene Reduces Post-ischemic Cerebral Neutrophil Accumulation, No-reflow, and Tissue Injury in a Murine Model of Reperfused **Stroke**

DETD Recent studies in humans indicate that reestablishment of cerebral blood flow (CBF) during the early period following the onset of **stroke** reduces neurologic sequelae. It was hypothesized that P-selectin (PS), an early-acting neutrophil (PMN) adhesion molecule expressed by hypoxic endothelium may have an important pathophysiological role in evolving, reperfused **stroke**. Preliminary studies were performed in a murine model of transient focal cerebral ischemia consisting of intraluminal middle cerebral artery occlusion. . . hours (n=7, $p<0.05$). The effect of PS expression on post-ischemic cerebral no-reflow was investigated by measuring ipsilateral CBF serially during **stroke** evolution. Although baseline, post-occlusion, and initial reperfusion CBFs were identical, CBFs at 30 minutes of reperfusion were

significantly greater in. . . period. These data support an important
early role for PS in PMN recruitment, post-ischemic no-reflow, and tissue damage in evolving **stroke**. This is the first demonstration of a pathophysiological role for PS in cerebral reperfusion injury, which suggests that PS blockade may represent a therapeutic target for the treatment of reperfused **stroke**.

DETD Carbon Monoxide and Evolving **Stroke**

DETD . . . oxygenase is induced during inflammatory conditions, it was investigated whether endogenous CO production may confer a cerebral protective role in **stroke**. In a murine model of focal cerebral ischemia, heme oxygenase type I was induced at the mRNA (by Northern blot). . . induction of heme oxygenase mRNA, protein and CO generation. To determine whether CO production was incidental to the pathophysiology of **stroke**, CO production was blocked by tin protoporphyrin administration (confirmed by direct measurement of reduced local CO levels). These animals demonstrated. . . significantly larger infarct volumes, worse neurological outcomes, and increased mortality compared with untreated controls. Furthermore, administration of CO prior to **stroke** conferred significant cerebral protection. As this protection was not observed in animals treated with biliverdin, the coincident byproduct of heme catabolism, these data suggest that endogenous CO production per se has a protective
role in evolving **stroke**.

DETD . . . produces large amounts of CO, the production of which confers cerebral protection that limits the amount of tissue destroyed during **stroke**.

DETD In **stroke** and other ischemic disorders, there may be clinical benefit derived by lysing an existing thrombus, but there is also the potentially devastating complication of hemorrhage. In the current experiments, the mouse model of cerebral ischemia and reperfusion (**stroke**) was used. Mice received an intravenous bolus of 300 .mu.g/kg of Factor IXai just prior to surgery. **Strokes** were created by intraluminal occlusion of the right middle cerebral artery. When **stroke** outcomes were measured 24 hours later, animals that had received Factor IXai had smaller infarct volumes, improved cerebral perfusion, less. . .

DETD . . . Injury In Mice Which Express the P-Selectin Gene: Identification of P-selectin Blockade as a New Target for the Treatment of **Stroke**

DETD There is currently a stark therapeutic void for the treatment of evolving **stroke**. Although P-selectin is rapidly expressed by hypoxic endothelial cells in vitro, the functional significance of P-selectin expression in **stroke** remains unexplored. In order to identify the pathophysiological consequences of P-selectin expression
and to identify P-selectin blockade as a potential new approach for the treatment of **stroke**, experiments were performed using a murine model of focal cerebral ischemia and reperfusion. Early P-selectin expression in the post-ischemic cerebral. . . ipsilateral cerebral microvascular endothelial cells by immunohistochemistry. In experiments designed to test the functional significance of increased P-selectin expression in **stroke**, neutrophil accumulation in the ischemic cortex of mice expressing the P-selectin gene (PS +/+) was demonstrated to be significantly greater. . . blockade of P-selectin in PS +/+ mice using a monoclonal antibody directed against murine P-selectin also
improved early reflow and **stroke** outcome compared with controls, with reduced cerebral infarction volumes noted even when the

blocking antibody was administered after occlusion of the middle cerebral artery. These data are the first to demonstrate a pathophysiological role for P-selectin in **stroke**, and suggest that P-selectin blockade may represent a new therapeutic target for the treatment of **stroke**.

DETD Ischemic **stroke** constitutes the third leading cause of death in the United States today.sup.1. Until very recently, there has been no direct treatment to reduce cerebral tissue damage in evolving **stroke**. Although the NINDS.sup.2 and ECAS.sup.3 S rt-PA.sup.2.dagger. acute **stroke** studies have suggested that there are potential therapeutic benefits of early reperfusion.sup.4, the increased mortality observed following streptokinase treatment of acute ischemic **stroke**.sup.5 highlights the sobering fact that there is at the present time no clearly effective treatment for evolving **stroke**. This void in the current medical armamentarium for the treatment of **stroke** has led to a number of innovative approaches.sup.6, yet other than rt-PA, none have reached the clinical realm. To identify a potential safe and efficacious treatment for evolving **stroke**, we have focussed on the deleterious role of recruited neutrophils. Recent work in a murine model of reperfused **stroke** has demonstrated that depletion of neutrophils (PMNs) prior to **stroke** minimizes cerebral tissue injury and improves functional outcome.sup.7 ; mice which lack the specific cell adhesion molecule, ICAM-1, are similarly. . . is an important early mediator of the neutrophil rolling.sup.9, which facilitates ICAM-1-mediated neutrophil arrest. Although P-selectin is expressed in primate **stroke**.sup.10, the functional significance of P-selectin expression in **stroke** remains unknown.

DETD To explore the pathophysiological role of P-selectin in **stroke** , we employed a murine model of focal cerebral ischemia and reperfusion.sup.11 using both wild type mice and mice which were. . . P-selectin expression following middle cerebral artery occlusion is associated with reduced cerebral reflow following reperfusion and a worse outcome following **stroke**, but that P-selectin blockade confers a significant degree of postischemic cerebral protection. These studies represent the first demonstration of the pathophysiological role of P-selectin expression in **stroke**, and suggest the exciting possibility that anti-P-selectin strategies may prove useful for the treatment of reperfused **stroke**.

DETD . . . the time of experiments. Because variations in cerebrovascular anatomy have been reported to result in differences in susceptibility to experimental **stroke** in mice.sup.12, India ink/carbon black staining was performed to visualize the the vascular pattern of the Circle of Willis in. . .

DETD . . . volumes has been used previously by our group.sup.7,11 and others.sup.16,17, and has been correlated with the other functional indices of **stroke** outcome which are described above.

DETD P-selectin Expression in Murine **Stroke**: Because P-selectin mediates the initial phase of leukocyte adhesion to activated endothelial cells.sup.20, we examined early cerebral P-selectin expression in a murine model of reperfused **stroke**. Mice given a .sup.125 I-labelled rat monoclonal anti-murine P-selectin IgG prior to surgery demonstrated a 216% increase in accumulation of. . .

DETD Neutrophil Accumulation in Murine **Stroke**: To delineate the time course over which PMN influx occurs following **stroke**,

.sup.111 In-labeled PMN accumulation was measured in wild type (PS +/+) mice prior to MCAO, immediately following and 10 minutes. . .

DETD **Stroke** Outcome: The functional significance of P-selectin expression was tested by comparing indices of **stroke** outcome in PS -/- mice to those in PS +/+ controls. PS -/- mice were significantly protected from the effects. . .

DETD Effect of P-selectin Blockade: After having observed the functional role of P-selectin expression in **stroke** using deletionally mutant mice, experiments were performed to determine whether pharmacological blockade of P-selectin could improve **stroke** outcome in PS +/+ mice. Using a strategy of administering a functionally blocking monoclonal rat anti-mouse P-selectin antibody (clone RB. . . leftmost 6 bars). To increase the potential clinical relevance of a strategy of P-selectin blockade as a new treatment for **stroke**, additional experiments were performed in which either the control or the blocking antibody were given after intraluminal occlusion of the middle cerebral artery (because most patients present following the onset of **stroke**). In these studies, a significant reduction in infarct volumes was observed as well as a trend towards improved cerebral blood.

. .

DETD Despite substantial progress in recent years in the primary prevention of **stroke**.sup.1, therepeutic options to treat evolving **stroke** remain extremely limited. Although the publication of two landmark trials last fall demonstrating reduced morbidity following treatment of ischemic **stroke** with rt-PA.sup.2,3 was thought to usher in a new era of thrombolytic therapy in the treatment of **stroke**.sup.4, enthusiasm has been tempered somewhat by the hemorrhagic transformation and increased mortality noted in patients with ischemic **stroke** treated with streptokinase.sup.5. These divergent trials make it more critical than ever that new safe therapies be developed to treat evolving **stroke**. Although restoration of blood flow to postischemic brain affords new opportunities for early therapeutic intervention, reperfusion is a double-edged sword.. . . is not surprising that neutrophil influx into postischemic brain tissue can lead to further damage and worsen outcome following experimental **stroke**.sup.7,24-27. Using a murine model of focal cerebral ischemia and reperfusion, we have recently identified an important contributory role for the cell adhesion molecule ICAM-1 in neutrophil accumulation at 22 hours following **stroke**.sup.7. However, augmented cerebrovascular endothelial ICAM-1 expression requires de novo transcriptional and translational events, which requires time. In contrast, P-selectin, a. . . storage pools to be rapidly expressed at the ischemic endothelial cell surface.sup.8,28. As the clinical trials of thrombolytic therapy for **stroke** demonstrate a narrow time window for potential benefit (within the first several hours of **stroke** onset).sup.2,3,5, this suggests that strategies designed to interfere with the earliest phases of PMN adhesion might be of theoretical benefit in human **stroke**. These trials should result in greater numbers of patients presenting for earlier therepeutic intervention, increasing the need to address the. . . territories. In addition, they underscore the pressing need to understand the contributions of individual adhesion molecules to the pathogenesis of

stroke.
DETD . . . role of P-selectin in other models of ischemia and reperfusion.sup.8,29-32, surprisingly little is known about the role of P-selectin in **stroke**. Knowledge of the specific role of P-selectin in the cerebral vasculature is important because adhesion molecule requirements vary between vascular. . .
DETD . . . our knowledge, the only published study describing increased P-selectin expression in the ischemic brain is a histopathological description of primate **stroke**, in which P-selectin expression was increased in the lenticulostriate microvasculature.sup.10. The current studies were undertaken to study whether P-selectin expression contributes to post-ischemic cerebral neutrophil accumulation, no-reflow, and tissue injury in a murine model of reperfused **stroke**. Using a recently established model of focal cerebral ischemia and reperfusion in mice.sup.11, P-selectin expression was demonstrated by increased endothelial. . . is augmented in the reperfused tissue. This data in the murine model parallels that reported in a baboon model of **stroke**.sup.10, in which P-selectin expression was increased within 1 hour following the ischemic event.
DETD . . . these data do not alter our main conclusions, that P-selectin is an important mediator of cerebral tissue injury in reperfused **stroke**.
DETD . . . with controls. When these data are considered along with previously published data demonstrating a deleterious role for ICAM-1 expression in **stroke**.sup.7, it becomes increasingly apparent that there are multiple means for recruiting PMNs to post-ischemic cerebral cortex, and that blockade of each represents a potential strategy to improve **stroke** outcome in humans. Given our current recognition of the importance of timely reperfusion in halting the advancing wavefront of neuronal death following **stroke**, interfering with PMN adhesion at its earliest stages appears to be an attractive option for reducing morbidity and mortality. In. . . of opportunity for thrombolytic intervention.sup.40. The current set of studies contributes to our understanding of pathophysiological mechanisms operative in reperfused **stroke**. These studies suggest the need for clinical trials of therapies for evolving **stroke** which optimize the reperfusion milieu to reduce PMN accumulation.
DETD 1. Bronner L L, Kanter D S, Manson J E: Primary prevention of **stroke**. N Engl J Med 1995;333(21):1392-1400
DETD 2. The National Institute of Neurological Disorders and **Stroke** rt-PA **Stroke** Study Group: Tissue plasminogen activator for acute ischemic **stroke**. N Engl J Med 1995;333:1581-1587
DETD . . . Mahagne M H, Hennerici M, for the ECASS Study Group: Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric **stroke**. J A M A 1995;274(13):1017-1025
DETD 4. del Zoppo G J: Acute **stroke**--on the threshold of a therapy. N Engl J Med 1995;333(13):1632-1633
DETD 5. Hommel M, Cornu C, Boutitie F, Boissel J P, The MultiCenter Acute **Stroke** Trial-Europe Study Group: Thrombolytic therapy with streptokinase in acute ischemic **stroke**. N Engl J Med 1996;335:145-150
DETD 6. Baringa M: Finding new drugs to treat **stroke**. Science 1996;272:664-666
DETD . . . Cerebral protection in homozygous null ICAM-1 mice after middle cerebral artery occlusion. Role of neutrophil adhesion in the pathogenesis of **stroke**. J Clin Invest 1996;97:209-216
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adhesion molecule-1 expression after focal brain ischemia and reperfusion. **Stroke** 1994;25:202-211

DETD . . . Dirnagl U, Kaplan B, Jacewicz M, Bulsinelli W: Continuous measurement of cerebral blood flow by laser-doppler flowmetry ion a rat **stroke** model. J Cereb Blood Flow Metab 1989;9:589-596

DETD . . . Bartkowski H M: Evaluation of 2,3,5-triphenyltetrazolium chloride as a stain for detection and quantification of experimental cerebral infarction in rats. **Stroke** 1986;17:1304-1308

DETD 22. Levy D E, Van Uitert R L, Pike C L: Delayed postischemic hypoperfusion: a potentially damaging consequence of **stroke**. Neurology 1979;29:1245-1252

DETD . . . T P, Contreras T J: Polymorphonuclear leukocyte accumulation in brain regions with low blood flow during the early postischemic period. **Stroke** 1986;17:246-253

DETD 25. Kochanek P M, Hallenbeck J M: Polymorphonuclear leukocytes and monocytes/macrophages in the pathogenesis of cerebral ischemia and **stroke**. **Stroke** 1992;23(9):1367-1379

DETD . . . Dutka A J, Kochanek P M, Hallenbeck J M: Influence of granulocytopenia on canine cerebral ischemia induced by air embolism. **Stroke** 1989;20:390-395

DETD . . . McAuliffe T, Lodge P A, Gross C E: The role of neutrophils and platelets in a rabbit model of thromboembolic **stroke**. **Stroke** 1991;22(1):44-50

DETD . . . D, Copeland B R, Arfors K E: Inhibition of polymorphonuclear leukocyte adherence suppresses no-reflow after focal cerebral ischemia in baboons. **Stroke** 1992;23:712-718

DETD Background and Purpose There is a great interest in developing novel anticoagulant or thrombolytic strategies to treat ischemic **stroke**. However, at present, there are limited means to accurately assess the hemorrhagic potential of these agents. The current studies were. . . artery occlusion/reperfusion was quantified in mice treated with post-occlusion high-dose IV rt-PA (10 mg/kg, n=11) and control mice subjected to **stroke** but treated with physiological saline solution (n=9). Results Known quantities of hemoglobin or autologous blood added to fresh whole brain. . . had significantly higher ODs than saline-infused controls (2.1-fold increase, p=0.05). In a middle cerebral artery occlusion and repersfusion model of **stroke**, administration of rt-PA after reperfusion increased the OD by 1.8-fold compared with animals which received physiological saline solution (p<0.001). When. . . ICH. This new method should aid objective assessment of the hemorrhagic risks of novel anticoagulant or thrombolytic strategies to treat **stroke** and can facilitate quantification of other forms of intracerebral hemorrhage.

DETD Ischemic **stroke** accounts for the greatest majority of presentations in acute **stroke**. There has thus been a tremendous interest in designing strategies which can promptly and effectively restore blood flow to the ischemic region of brain. Although heparin may be effective in incipient **stroke** (TIAs).sup.3, its use during the acute phases of **stroke** may be associated with a high degree of morbidity and intracerebral hemorrhage.sup.1-4. Similarly, in the early 1960s, the dismal outcomes in the streptokinase trials for acute **stroke** led to the reluctance of clinicians to thrombolyse acute **stroke** for the subsequent three decades.sup.5,6. This reluctance has been validated by recent trials in

which the use of streptokinase has. . . risk of mortality and intracerebral hemorrhage.sup.7. On the other hand, the use of recombinant tissue-type plasminogen activator (rt-PA) to treat **stroke**-in-progress has shown more promise.sup.8, with a subset of patients with acute **stroke** who are treated with rt-PA demonstrating reduced long-term morbidity if treated within the first 3 hours of symptom onset.sup.9-11. Even. . .

DETD . . . Towards this end, it is imperative to identify an experimental model in which the potential benefits of timely reperfusion in **stroke** can be weighed objectively against the risks of increased intracerebral hemorrhage. In most animal studies of thrombolytic therapy for clinical **stroke**, the risks of intracerebral hemorrhage have been estimated rather than quantitatively measured.sup.16-24. The current studies were designed to develop and. . . of intracerebral hemorrhage in murine models, in order to assess potential risks of new anticoagulant or thrombolytic treatments for acute **stroke**.

DETD . . . removal of the occluding suture, animals received either intravenous tissue plasminogen activator (10 mg/kg in 0.2 ml normal saline solution, **Stroke**+rt-PA) or normal saline solution (**Stroke**+Saline) given by dorsal penile vein injection. At 24 hours, brain tissue was harvested immediately after rapid anesthetized decapitation. To evaluate. . .

DETD . . . of ICH were performed using Pearson's linear correlation, with correlation coefficients indicated. To establish whether a given treatment (Collagenase, Sham, **Stroke**, etc.) had a significant effect on either spectrophotometric or visually-scored ICH, comparisons were made using an unpaired two-tailed t-test. For. . .

DETD In the second and perhaps more clinically relevant method for inducing ICH, a **stroke** was created by transient intraluminal occlusion of the middle cerebral artery followed by reperfusion. In addition, we attempted to increase. . . rt-PA immediately following removal of the intraluminal occluding suture. These data indicate that the addition of a fibrinolytic agent following **stroke** increases the amount of ICH which is detected by the spectrophotometric hemoglobin assay [FIG. 36B]. It is interesting to note that baseline absorbance is lower in animals subjected to **stroke** than control/untreated animals [FIGS. 36A and 36B]. To further investigate how residual intravascular blood might affect the spectrophotometric hemoglobin assay,. . . subjected to either no or sham surgery (n=10, OD 0.34.+-.0.05, p=0.05 vs cardiac perfused controls). On the other hand, following **stroke** , there was no difference in O.D. whether or not cardiac saline perfusion was performed (0.15.+-.0.04 for **stroke** without cardiac saline perfusion, n=5; 0.15.+-.0.03 for **stroke** with cardiac saline perfusion, P=NS). When saline-perfused animals with **stroke** were compared to saline-perfused animals without **stroke**, there is an apparent reduction in OD following spectrophotometric hemoglobin assay. These data would suggest that animals with a **stroke** have less intracerebral blood detected, perhaps as the result of a reduction of the total amount of blood in the. . .

DETD . . . either collagenase alone or collagenase+rt-PA was added to the infusate, visual ICH scores were significantly increased [FIG. 38A]. In the **stroke** model, rt-PA similarly resulted in an increase in the visual ICH score [FIG. 38B]. When the data are plotted to. . .

DETD Recently, it has become apparent that early intervention in **stroke** with certain intravenous thrombolytic agents (rt-PA) may be beneficial if instituted within 3 hours of symptom onset.sup.9,10.

However, administration of. . .
DETD . . . reliability using known quantities of hemoglobin and autologous
blood admixed with brain tissue.sup.31. Because the surgical procedure used in the **stroke** experiments did not significantly alter blood hemoglobin concentrations (data not shown), the spectrophotometric
hemoglobin assay may be used to extrapolate. . .
DETD . . . (to weaken the vascular wall, as might occur with an aneurysm or with trauma; and (2) in a model of **stroke**. In both instances, a cohort of animals also received rt-PA, in order to validate
the model at the high end. . . ICH size as independently assessed by visual scoring. Finally, to prove the assay even more useful for experimental models of **stroke** in which brains are stained with triphenyltetrazolium chloride (TTC) to quantify cerebral infarct volume,
the brains of animals subjected to. . .
DETD . . . brain harvest. The procedure of cephalic saline perfusion does not alter the optical density for cyanomethemoglobin in brain subjected to **stroke**, suggesting that the amount of intravascular blood is relatively fixed and does not wash out by the procedure. However, in.
. . cyanomethemoglobin by about 30%. Our experiments do not provide the reason for this difference, but one may speculate that following **stroke**, there is an element of vasoconstriction/vaso-occlusion in the territory of infarction, which makes the saline perfusion technique less effective at washing out additional residual intravascular blood. Also, if there is truly an element of vasoconstriction following **stroke** or experimentally-induced intracerebral hemorrhage, this may reduce the intravascular blood pool and hence account for an overall lowering of the optical density when control and **stroke**/ICH brains are compared (even if some extravascular blood is present in the latter group).
DETD . . . should prove especially useful to evaluate the hemorrhagic potential of newly developed thrombolytic or anticoagulant therapies for
the treatment of **stroke**.
DETD 1. Slivka A, Levy, D: Natural history of progressive ischemic **stroke** in a population treated with heparin. **Stroke** 1990;21:1657-1662
DETD 2. Babikian V L, Kase C S, Pessin M S, Norrving B, Gorelick P B: Intracerebral hemorrhage in **stroke** patients anticoagulated with heparin. **Stroke** 1989;20:1500-1503
DETD 3. Ramirez-Lassepas M, Quinones M R, Nino H H: Treatment of acute ischemic **stroke**. Open trial with continuous intravenous heparinization. Arch Neurol 1986;43:386-390
DETD 4. Duke R J, Bloch R F, Turpie A G, Trebilcock R, Bayer N: Intravenous heparin for the prevention of **stroke** progression in acute partial stable **stroke**. Annals of Internal Medicine 1986;105:825-828
DETD 6. Meyer J S, Gilroy J, Barnhart M I, Johnson J F: Anticoagulants plus streptokinase therapy in progressive **stroke**. JAMA 1964;189:373
DETD 7. Hommel M, Cornu C, Boutitie F, Boissel J P, The MultiCenter Acute **Stroke** Trial--Europe Study Group: Thrombolytic therapy with streptokinase in acute ischemic **stroke**. N Engl J Med 1996;335:145-150
DETD 8. Wardlaw J M, Warlow C P: Thrombolysis in acute ischemic **stroke**: does it work? **Stroke** 1992;23:1826-1839
DETD 9. The National Institute of Neurological Disorders and **Stroke**

rt-PA **Stroke** Study Group: Tissue plasminogen activator for acute ischemic **stroke**. N Engl J Med 1995;333:1581-1587

DETD . . . Mahagne M H, Hennerici M, for the ECASS Study Group: Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric **stroke**. J A M A 1995;274(13):1017-1025

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DETD . . . M, Kleinholz M, Holm P, DeVoe G, Schmitt G, Wagner K R, Myers R E: Hemorrhagic infarct conversion in experimental **stroke**. Ann Emerg Med 1992;21:120-126

DETD 17. Overgaard K, Sereghy T, Pedersen H, Boysen G: Neuroprotection with NBQX and thrombolysis with rt-PA in rat embolic **stroke**. Neurological Research 1993;15:344-349

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DETD . . . R F: Effect of intra-arterial tissue plasminogen activator and urokinase on autologous arterial emboli in the cerebral circulation of rabbits. **Stroke** 1990;21:1594-1599

DETD 20. Overgaard K, Sereghy T, Pedersen H, Boysen G: Effect of delayed thrombolysis with rt-PA in a rat embolic **stroke** model. Journal of Cerebral Blood Flow & Metabolism 1994;14:472-477

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DETD 23. Slivka A, Pulsinelli W: Hemorrhagic complications of thrombolytic therapy in experimental **stroke**. **Stroke** 1987;18:1148-1156

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correlates. **Stroke** 1996;27:2312-2320

DETD . . . J, Brendel R: Magnetic resonance imaging study on the effect of
levemopamil on the size of intracerebral hemorrhage in rats. **Stroke** 1994;25:1836-1841

DETD Active-site Blocked Factor IXa Limits Microvascular Thrombosis and Cerebral Injury In Murine **Stroke** Without Increasing Intracerebral Hemorrhage

DETD The clinical dilemma in **stroke** treatment is that agents which restore vascular patency increase the risk of intracerebral hemorrhage. Active-site blocked Factor IXa (IXai), formed. . .

DETD Administration of Factor IXai represents a new strategy to treat **stroke** in evolution without increasing the risk of intracerebral hemorrhage.

DETD Timely reestablishment of blood flow to ischemic brain represents the current treatment paradigm for acute **stroke**.sup.1-3. Administration of a thrombolytic agent, even when given under optimal conditions, may not achieve this desired clinical result. Perfusion often. . . solely by the original occlusion, but that there is also an element of microcirculatory failure. In addition, thrombolysis of acute **stroke** is associated with an increased risk of intracerebral hemorrhage (ICH).sup.1-4, indicating that there remains a clear need to identify new. . .

DETD . . . vascular wall is modified from its quiescent, anti-adhesive, antithrombotic state, to one which promotes leukocyte adhesion and thrombosis. In acute **stroke**, active recruitment of leukocytes by adhesion receptors expressed in the ipsilateral microvasculature, such as ICAM-1.sup.5 and P-selectin.sup.6, potentiates postischemic hypoperfusion.. . . the hypothesis that local thrombosis occurs at the level of the microvasculature (distal to the site of primary occlusion) in **stroke**.

DETD To assess the deleterious consequences of microvascular thrombosis in **stroke**, the second set of experiments tested the hypothesis that selective blockade of the intrinsic pathway of coagulation could limit microvascular thrombosis, thereby protecting the brain in **stroke** . The strategy of selective inhibition of the intrinsic pathway of coagulation was chosen because it is primarily responsible for intravascular. . . strategy in which a competitive inhibitor of Factor IXa (active-site blocked IXa, or IXai) was given to mice subjected to **stroke** to test the hypothesis that is would improve **stroke** outcome without increasing ICH.

DETD Murine **stroke** model: Transient focal cerebral ischemia was induced in mice by intralumenal occlusion of the middle cerebral artery (45 minutes) and. . .

DETD To crate a **stroke** in a murine model, a suture is introduced into the cerebral vasculature so that it occludes the orifice of the. . . rendering the subtended territory ischemic. By withdrawing the . suture after a 45 minute period of occlusion, a reperfused model of **stroke** is created; mice so treated demonstrate focal neurological deficits as well as clear-cut areas of cerebral infarction.

Because the occluding. . . deposition during the ensuing period of cerebral ischemia and reperfusion. In animals not subjected to the surgical procedure to create **stroke**, the presence of platelets was approximately equal between the right and left hemispheres, as would be expected [FIG. 40A, left bar]. However, when animals were subjected to **stroke** (and received only vehicle to control for subsequent

experiments), radiolabeled platelets preferentially accumulated in the ischemic (ipsilateral) hemisphere, compared with. . .

DETD Another line of evidence also supports the occurrence of microvascular thrombosis in **stroke**. This data comes from the immunodetection of fibrin, using an antibody directed against a neoepitope on the gamma--gamma chain dimer. . . subjected to focal cerebral ischemia and reperfusion [FIG. 40B, "Vehicle"]. In animals treated with Factor IXai (300 .mu.g/kg) prior to **stroke**, there is no apparent increase in the ipsilateral accumulation of fibrin [FIG. 40B, "Factor IXai"]. To demonstrate that fibrin accumulation. . .

DETD To investigate whether Factor IXai can limit intracerebral thrombosis and restore perfusion IXai was given to mice immediately prior to **stroke** (300 .mu.g/kg). These experiments demonstrate both a reduction in .sup.111 In-platelet accumulation in the ipsilateral hemisphere [FIG. 41A] as well. . .

DETD Because the development of ICH is a major concern with any anticoagulant strategy in the setting of **stroke**, the effect of IXai on ICH was measured using our recently validated spectrophotometric method for quantifying ICH.sup.11,12. These data indicate. . .

DETD Because therapies directed at improving outcome from acute **stroke** must be given after clinical presentation, and because fibrin continues to form following the initial ischemic event in **stroke**, we tested whether IXai might be effective when given following initiation of cerebral ischemia. IXai given after middle cerebral artery. . .

DETD . . . of intravascular thrombus formation (both platelets and fibrin) within the post-ischemic cerebral microvasculature. The pathophysiological relevance of microvascular thrombosis in **stroke** is underscored by the ability of Factor IXai to reduce microvascular thrombosis (both platelet and fibrin accumulation are reduced, with an attendant increase in postischemic CBF) and to improve **stroke** outcome. These potent antithrombotic actions of Factor IXai are likely to be clinically significant in the setting of **stroke**, because Factor IXai not only reduces infarct volumes in a dose-dependent manner, but it does so even when given after the onset of **stroke**. In addition, at clinically relevant doses, treatment with Factor IXai does not cause an increase in ICH, making selective inhibition of Factor IXa/VIIIa/X activation complex assembly with Factor IXai an attractive target for **stroke** therapy in humans.

DETD . . . targetted anticoagulant strategies might be an attractive alternative to the current use of thrombolytic agents in the management of acute **stroke**, because of their checkered success in clinical trials. Theoretically, an ideal treatment for acute **stroke** would prevent the formation or induce dissolution of the fibrin-platelet mesh that causes microvascular thrombosis in the ischemic zone without increasing the risk of intracerebral hemorrhage. However, thrombolytic agents which have been studied in clinical trials of acute **stroke** have consistently increased the risk of intracerebral hemorrhage .sup.1-4. Streptokinase, given in the first several (<6) hours following **stroke** onset, was associated with an increased rate of hemorrhagic transformation (up to 67%); although here was increased early mortality, surviving patients suffered less residual disability. Administration of tissue-type plasminogen activator (tPA) within 7 hours (particularly within 3 hours) of **stroke** onset resulted in increased early mortality and increased rates of hemorrhagic conversion (between 7-20%), although survivors demonstrated

less residual disability. In order to develop improved anticoagulant or thrombolytic therapies, several animal models of **stroke** have been examined. These models generally consist of the administration of clotted blood into the internal carotid artery followed by administration of a thrombolytic agent. In rats, tPA administration within 2 hours of **stroke** improved cerebral blood flow and reduced infarct size by up to 77%.sup.14,15. In a similar rabbit embolic **stroke** model, tPA was effective at restoring blood flow and reducing infarct size, with occasional appearance of intracerebral hemorrhage.sup.16,17. However, although. . .

DETD Because of the usually precipitous onset of ischemic **stroke**, therapy has been targetted primarily towards lysing the major fibrinous/atheroembolic debris which occludes a major vascular tributary to the brain.. . . original occlusion, which is likely to be of considerable pathophysiological significance for post-ischemic hypoperfusion (no-reflow) and cerebral injury in evolving **stroke** . This data is in excellent agreement with that which has been previously reported, in which microthrombi have been topographically localized. . . reduces microvascular platelet and fibrin accumulation, improves postischemic cerebral blood flow, and reduces cerebral infarct volumes in the setting of **stroke** without increasing ICH.

DETD . . . the coagulation cascade. Not only does a strategy of Factor IXa blockade appear to be effective in the setting of **stroke**, but it also appears to be effective at preventing progressive coronary artery occlusion induced following the initial application of electric. . .

DETD The data which demonstrates that IXai given after the onset of **stroke** is effective leads to another interesting hypothesis, that the formation of thrombus represents a dynamic equilibrium between the processes of. . . The data in the current studies, which show that Factor IXai is effective even when administered after the onset of **stroke**, suggests that this strategy restores the dynamic equilibrium, which is shifted after cerebral ischemia to favor thrombosis, back towards a. . .

DETD . . . from the perspective of leukocyte adhesion receptor expression, even when these adhesion receptors are absent, CBF levels are improved following **stroke** compared with controls but do not return to preischemic levels. Taken together, these data suggests that microvascular thrombosis and leukocyte. . .

DETD . . . administration of a competitive inhibitor of Factor IXa, active-site blocked Factor IXa, represents a novel therapy for the treatment of **stroke**. This therapy not only reduces microcirculatory thrombosis, improves postischemic cerebral blood flow, and reduces cerebral tissue injury following **stroke**, but it can do so even if given after the onset of cerebral ischemia and without increasing the risk of. . . downside risk of hemorrhagic transformation makes this an extremely attractive approach for further testing and potential clinical trials in human **stroke**.

DETD 1. The National Institute of Neurological Disorders and **Stroke** rt-PA **Stroke** Study Group: Tissue plasminogen activator for acute ischemic **stroke**. New Engl J Med 1995;333:1581-1587

DETD . . . Mahagne M H, Hennerici M, for the ECASS Study Group: Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric **stroke**. J A M A 1995;274(13):1017-1025

DETD 3. del Zoppo G J: Acute **stroke**--on the threshold of a therapy. N Engl J Med 1995;333(13):1632-1633

DETD 4. Hommel M, Cornu C, Boutitie F, Boissel J P, The MultiCenter Acute **Stroke** Trial--Europe Study Group: Thrombolytic therapy with streptokinase in acute ischemic **stroke**. N Engl J Med 1996;335:145-150

DETD . . . Cerebral protection in homozygous null ICAM-1 mice after middle cerebral artery occlusion. Role of neutrophil adhesion in the pathogenesis of **stroke**. J Clin Invest 1996;97:209-216

DETD . . . injury in mice which express the P-selectin gene: identification of P-selectin blockade as a new target for the treatment of **stroke**. Example 10 Hereinabove

DETD . . . W F, Salamat M S, Topol E J, Sackellares J C: Recombinant human tissue-type plasminogen activator therapy in acute thromboembolic **stroke**. J Neurosurg 1987;67:394-398

DETD 15. Overgaard K, Sereghy T, Pedersen H, Boysen G: Neuroprotection with NBQX and thrombolysis with rt-PA in rat embolic **stroke**. Neurol Res 1993;15:344--349

DETD . . . A N, Orozco J, Temeltas O: Influence of tissue plasminogen activator and heparin on cerebral ischemia in a rabbit model. **Stroke** 1992;23:883-888

DETD . . . A, Smith T W, Pang R H L: Delayed treatment with a t-PA analogue and streptokinase in a rabbit embolic **stroke** model. **Stroke** 1990;21:602-605

CLM What is claimed is:

. . . thrombosis, a myocardial infarction, a transient ischemic attack, unstable angina, a reversible ischemic neurological deficit, sickle cell anemia or a **stroke** disorder.

AB The present invention provides for a method of treating an ischemic disorder in a subject which comprises administering to the subject a pharmaceutically acceptable form of inactivated Factor IX in a sufficient amount over a sufficient period of time to inhibit coagulation so as to treat the ischemic disorder in the subject.

L7 ANSWER 2 OF 21 USPATFULL

PI US 6136821 20001024
WO 9818796 19980507 <--

DETD . . . isoenzymes, in particular their profile as selective type 4 inhibitors, AGENTS OF THE INVENTION are further useful as type 4 **PDE inhibitors**, for example for the treatment of disease involving tissue calcium depletion, in particular degenerative diseases of the bone and joint. . . treatment of other conditions where inhibition of PDE 4 is indicated, for example, depression, conditions and diseases characterized by impaired **cognitive** function including Alzheimer's disease, Parkinson's disease and **stroke**.

AB Novel 8-aryl-1,7-naphthyridines, in free or salt form, are PDE IV inhibitors and are thus useful as pharmaceuticals, e.g. for asthma therapy. Preferred compounds include compounds of formulae (I and II) wherein the R groups are as defined. Pharmaceutical compositions comprising the compounds, processes for preparation of the compounds and novel intermediates for use in the processes are disclosed.

L7 ANSWER 3 OF 21 USPATFULL

PI US 6136810 20001024

WO 9719078 19970529 <--

SUMM This invention relates to novel pyrido[2,3-d]pyrimidine derivatives useful as medicines, particularly as type IV **phosphodiesterase inhibitors**, pharmaceutically acceptable salts thereof, pharmaceutical compositions thereof, use thereof for the production of medicaments and a preventing or treating method. . .

SUMM Also, it has been reported that a type IV **PDE inhibitor** shows an action to inhibit eosinophiles infiltration by antigen and platelet activating factor in guinea pigs [Eur. J. Pharmacol., 255,. . .

SUMM . . . is characterized in that a compound having a pyrido[2,3-d]pyrimidine structure is provided for the first time as a type IV **PDE inhibitor**.

SUMM . . . or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. Embodiments of the pharmaceutical composition includes a type IV **PDE inhibitor** which contains the compound (I), preferably the compound (III), or a pharmaceutically acceptable salt thereof, more particularly an agent for. . .

SUMM Also included in the present invention is a type IV **PDE inhibitor** which contains the compound (II) or a pharmaceutically acceptable salt thereof, more particularly an agent for use in the prevention. . .

SUMM diseases related to nervous function abnormality (e.g., learning, memory and **cognition** disturbances related to nervous degeneration diseases such as Alzheimer disease, Parkinson disease and the like, multiple lateral sclerosis, senile dementia,. . .

SUMM . . . protection of nerves and cells [e.g., cardiac arrest, spinal cord injury, intermittent claudication, ischemic diseases (e.g., angina pectoris, myocardial infarction, **stroke**, head injury and the like) and the like],

SUMM . . . Gram negative bacillus sepsis, toxic shock syndrome, nephritis, hepatitis, infection (bacterial and viral), circulatory failure (heart failure, arteriosclerosis, myocardial infarction, **stroke**) and the like],

SUMM . . . Gram negative bacillus sepsis, toxic shock syndrome, nephritis, hepatitis, infection (bacterial and viral), circulatory failure (heart failure, arteriosclerosis, myocardial infarction, **stroke**) and the like].

SUMM Also, since the compounds of the present invention show extremely weak vomiting action in comparison with the prior **phosphodiesterase inhibitors**, they are particularly useful for the treatment or prevention of diseases in patients who require systemic administration.

CLM What is claimed is:

9. A pharmaceutical composition for a type IV **phosphodiesterase inhibitor** which comprises a pyrido[2,3-d]pyrimidine derivative according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof,. . .

AB This invention relates to compounds (I) or pharmaceutically acceptable salts thereof, having a function to inhibit type IV phosphodiesterase (PDE) ##STR1## [X: an oxygen atom or a sulfur atom, R.sup.1 : a lower alkyl group, a cycloalkyl-lower alkyl group or a cycloalkyl group,

R.sup.2 : a hydrogen atom, a halogen atom, a lower alkyl group, a halogeno-lower alkyl group, a hydroxy-lower alkyl group, a mercapto-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkylthio-lower alkyl group, a lower alkanoyloxy-lower alkyl group, a

lower alkanoylthio-lower alkyl group, a lower alkanoyl-lower alkyl group, a hydroxyimino-lower alkyl group, a lower alkoxyimino-lower alkyl group, a cycloalkyl group, an aryl group or a lower alkanoyl group,

R.sup.3 : a hydrogen atom, a halogen atom or a lower alkyl group,

R.sup.4 : a hydrogen atom or a lower alkyl group,

R.sup.5 : a cycloalkyl group; a naphthyl group substituted; a five- or six-membered monocyclic hetero ring group having 1 to 4 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom; or a group represented by the formula ##STR2## amd F.sup.6 : a halogen atom, a lower alkyl group, a halogeno-lower alkyl group, a hydroxyl group, a lower alkoxy group, a cyano group or a nitro group].

L7 ANSWER 4 OF 21 USPATFULL
TI Phenylpyridine derivatives useful as **phosphodiesterase inhibitors**
PI US 6090817 20000718
WO 9732853 19970912
DETD . . . isoenzymes, in particular their profile as selective type IV inhibitors, AGENTS OF THE INVENTION are further useful as type IV **PDE inhibitors**, for example for the treatment of disease involving tissue calcium depletion, in particular degenerative diseases of the bone and joint. . . treatment of other conditions where inhibition of PDE IV is indicated, for example, depression, conditions and diseases characterized by impaired **cognitive** function including Alzheimer's disease, Parkinson's disease and **stroke**.
AB (4-oxy-3-(aryl)phenyl)pyridine compounds, in free or acid addition salt form, are useful as pharmaceuticals for treatment and prophylaxis of inflammation, particularly inflammatory or obstructive diseases of the airways, e.g. for asthma therapy. Preferred compounds are novel biphenyl pyridines, biphenyl benzamides and biphenyl phenylcarboxy compounds. The compounds are selective inhibitors of PDE 4 isoenzyme activity and also act to down regulate or inhibit TNF-.alpha. release.

L7 ANSWER 5 OF 21 USPATFULL
PI US 5981535 19991109 <--
SUMM . . . ischaemia and are therefore useful in the treatment of cerebral vascular and neuronal degenerative disorders associated with learning, memory and **cognitive** dysfunctions including cerebral senility, multi-infarct dementia, senile dementia of the Alzheimer type, age associated memory impairment and certain disorders associated. . .
SUMM . . . in the prophylaxis of disorders associated with neuronal degeneration resulting from ischaemic events, including cerebral ischaemia due to cardiac arrest, **stroke** and also after cerebral ischaemic events such as those resulting from surgery and/or during childbirth. In addition treatment with the. . .
SUMM These compounds also act as **phosphodiesterase inhibitors** and elevate cyclic AMP levels and are therefore of potential use in the treatment of proliferative skin disease in human. . .
AB A method for the treatment of cerebrovascular disorders and/or disorders associated with cerebral senility and/or allergic disorders,

proliferative skin disorders, and bronchodilation which method comprises
the administration of an effective, non-toxic amount of a compound of formula (I): ##STR1## or if appropriate a pharmaceutically acceptable salt thereof, wherein R.sup.1 and R.sup.2 each independently represent alkyl or a moiety of formula (a):

--(CH.sub.2).sub.m --A (a)

wherein m represents zero or an integer 1, 2 or 3; A represents a substituted or unsubstituted cyclic hydrocarbon radical; and

R.sup.3 represents a halogen atom, a nitro group, or a group --NR.sup.4 R.sup.5 wherein R.sup.4 and R.sup.5 each independently represents hydrogen, alkyl or alkylcarbonyl or R.sup.4 and R.sup.5 together with the nitrogen to which they are attached forming an optionally substituted, heterocyclic group; certain novel compounds falling within formula (I) and compositions comprising such compounds.

L7 ANSWER 6 OF 21 USPATFULL
PI US 5817670 19981006 <--
WO 9606843 19960307 <--
SUMM The present invention also relates to a type IV **phosphodiesterase inhibitor** which comprises, as its active ingredient, a 1,8-naphthyridine derivative represented by the following general formula (I), a salt thereof, a. . .
SUMM Illustratively, the type IV **phosphodiesterase inhibitor** of the present invention is useful as an agent for prevention or treatment of respiratory diseases (for example, bronchial asthma. . .
SUMM . . . Gram negative bacillus sepsis, toxic shock syndrome, nephritis,
hepatitis, infection (bacterial and viral), circulatory failure (heart failure, arteriosclerosis, myocardial infarction, **stroke**) and the like.
SUMM . . . Gram negative bacillus sepsis, toxic shock syndrome, nephritis,
hepatitis, infection (bacterial and viral), circulatory failure (heart failure, arteriosclerosis, myocardial infarction, **stroke**) and the like).
SUMM diseases related to nervous function abnormality (e.g., learning, memory
and **cognition** disturbances related to nervous degeneration diseases such as Alzheimer disease, Parkinson disease and the like, multiple lateral sclerosis, senile dementia,. . .
SUMM . . . protection of nerves and cells (e.g., cardiac arrest, spinal cord injury, intermittent claudication, ischemic diseases (e.g., angina pectoris, myocardial infarction, **stroke**, head injury and the like) and the like),
SUMM . . . Gram negative bacillus sepsis, toxic shock syndrome, nephritis,
hepatitis, infection (bacterial and viral), circulatory failure (heart failure, arteriosclerosis, myocardial infarction, **stroke**) and the like),
SUMM . . . Gram negative bacillus sepsis, toxic shock syndrome, nephritis,
hepatitis, infection (bacterial and viral), circulatory failure (heart failure, arteriosclerosis, myocardial infarction, **stroke**) and the like).
SUMM Also, since the compounds of the present invention show extremely weak

vomiting action in comparison with the prior type IV **phosphodiesterase inhibitors**, they are particularly useful for the treatment or prevention of diseases in patients who require systemic administration.

CLM What is claimed is:

15. The pharmaceutical composition according to claim 14, which is a type IV **phosphodiesterase inhibitor**.

16. The pharmaceutical composition according to claim 15, which is a type IV **phosphodiesterase inhibitor** that is a preventive or therapeutic agent for respiratory diseases comprising bronchial asthma, chronic bronchitis, pneumonia and adult respiratory distress. . .

17. The pharmaceutical composition according to claim 15, which is a type IV **phosphodiesterase inhibitor** that is a preventive or therapeutic agent for inflammatory diseases comprising atopic dermatitis, conjunctivitis, urticaria, acquired immunodeficiency syndrome (AIDS), keloid. . .

AB 1,8-Naphthyridine derivatives represented by the following general formula (I), salts thereof, hydrates thereof and solvates thereof. ##STR1## They have an activity to inhibit type IV phosphodiesterase and are useful as agents for the prevention and treatment of respiratory diseases, inflammatory diseases accompanying organ transplantation, systemic or local arthropathy, proliferative diseases, micturition-related diseases and diseases in which tumor necrosis factor (TNF) and other cytokine (IL-1, IL-6 or the like) are concerned.

L7 ANSWER 7 OF 21 USPATFULL

PI US 5773423 19980630 <--

DETD . . . in accordance with the present inventive method include inflammatory disorders, such as vascular inflammation and arthritis, allergies, asthma, wound healing, **stroke**, cardiac failure, acute spinal cord injury, acute head injury or trauma, seizure, neonatal hypoxia (cerebral palsy; prophylactic treatment involves chronic. . .

DETD . . . compounds can be used to treat and/or protect against a variety of disorders, including, for example, seizures, transient ischemic shock, **strokes**, focal ischemia originating from thrombus or cerebral hemorrhage, global ischemia originating from cardiac arrest, trauma, neonatal palsy, hypovolemic shock, and. . . elicitation of such an effect would prove useful, such as in the treatment of Alzheimer's disease and other dementing and **cognitive** disorders.

DETD . . . After addition of 5 ml of lysis buffer, cells were mechanically scraped and homogenized in an ice-cold Dounce homogenizer (20 **strokes** by hand). The suspension was centrifuged at 43,000.times.g for 10 min. The pellet was resuspended in the minimum volume of. . .

DETD . . . Flow Metab., I, 729-738 (1987); Welsh et al., J. Cereb. Blood Flow Metab., 10, 557-563 (1990); and Minamisawa et al., **Stroke**, 21, 758-764 (1990). The temperature of the animals dropped by approximately 1.degree. C. over the course of the monitoring period.

DETD . . . the addition of [a-.sup.32 P]ATP to membranes in the presence of forskolin to stimulate adenylate cyclase and papaverine as a **phosphodiesterase inhibitor**. The reaction was terminated by addition of a stop solution containing 20,000 cpm/ml [.sup.3 H]cyclic AMP. The total radiolabeled cyclic. . .

AB The present invention provides N.sup.6 -benzyladenosine-5'-N-uronamide and related substituted compounds, particularly those containing substituents on the benzyl and/or uronamide groups, and modified xanthine ribosides, as well as pharmaceutical compositions containing such compounds. The present invention also provides a method of selectively activating an A.sub.3 adenosine receptor in a mammal, which method comprises acutely or chronically administering to a mammal in need of selective activation of its A.sub.3 adenosine receptor a therapeutically effective amount of a compound which binds with the A.sub.3 receptor so as to stimulate an A.sub.3 receptor-dependent response.

L7 ANSWER 8 OF 21 USPATFULL
PI US 5747506 19980505 <--
DETD . . . isoenzymes, in particular their profile as selective type IV inhibitors, AGENTS OF THE INVENTION are further useful as type IV **PDE inhibitors**, for example for the treatment of disease involving tissue calcium depletion, in particular degenerative diseases of the bone and joint. . . treatment of other conditions where inhibition of PDE IV is indicated, for example, depression, conditions and diseases characterized by impaired **cognitive** function including Alzheimer's disease, Parkinson's disease and **stroke**.
AB Compounds of formula I ##STR1## their physiologically-hydrolyzable and -acceptable esters and salts thereof. Said compounds, esters and pharmaceutically acceptable acid addition salts are useful as pharmaceuticals, e.g. for asthma therapy.

L7 ANSWER 9 OF 21 USPATFULL
PI US 5734051 19980331 <--
SUMM . . . ischaemia and are therefore useful in the treatment of cerebral vascular and neuronal degenerative disorders associated with learning, memory and **cognitive** dysfunctions including cerebral senility, multi-infarct dementia, senile dementia of the Alzheimer type, age associated memory impairment and certain disorders associated. . .
SUMM . . . in the prophylaxis of disorders associated with neuronal degeneration resulting from ischaemic events, including cerebral ischaemia due to cardiac arrest, **stroke** and also after cerebral ischaemic events such as those resulting from surgery and/or during childbirth. In addition treatment with the. . .
SUMM These compounds also act as **phosphodiesterase inhibitors** and elevate cyclic AMP levels and are therefore of potential use in the treatment of proliferative skin disease in human. . .
AB A method for the treatment of cerebrovascular disorders and/or disorders associated with cerebral senility and/or other disorders which method comprises the administration of an effective, non-toxic amount of a compound of formula (I): ##STR1## or if appropriate a pharmaceutically acceptable salt thereof, wherein R.sup.1 and R.sup.2 each independently represent alkyl or a moiety of formula (a):

--(CH.sub.2).sub.m --A (a)

wherein

m represents zero or an integer 1, 2 or 3;

A represents a substituted or unsubstituted cyclic hydrocarbon radical;

and

R.sup.3 represents a halogen atom, a nitro group, or a group --NR.sup.4 R.sup.5 wherein R.sup.4 and R.sup.5 each independently represents hydrogen, alkyl or alkylcarbonyl or R.sup.4 and R.sup.5 together with the nitrogen to which they are attached forming an optionally substituted, heterocyclic group; certain novel compounds falling within formula (I) and compositions comprising such compounds.

L7 ANSWER 10 OF 21 USPATFULL
PI US 5545651 19960813 <--
DETD . . . or bypass surgery, vascular hypertrophy and hyperplasia, atheroma and Raynaud's disease; cerebrovascular disorders such as migraine, and ischemic and hemorragic **stroke**; renal disorders such as renal vascular hypertension, proteinuria of primary renal disease, end stage renal disease and renal transplant therapy, glomerulonephritis, nephrotic syndrome, scleroderma and glomerular sclerosis, and for enhancing renal blood flow; CNS disorders such as impairment of **cognitive** function and memory loss, addiction, anxiety, bulimia, depression, epilepsy, pain, Parkinson's disease, psychosis, sleep disorders and tardive dyskinesia; ocular disorders. . .
DETD . . . of congestive heart failure include, in addition, compounds of this invention with cardiac stimulants such as dobutamine and xamoterol and **phosphodiesterase inhibitors** including atarinone and milrinone.
AB Novel substituted imidazoles of Formula (I), which are useful as angiotensin II antagonists, are disclosed: ##STR1##

L7 ANSWER 11 OF 21 USPATFULL
PI US 5409934 19950425 <--
WO 9211260 19920709 <--
SUMM It has been discovered that a novel series of sulphonated xanthines have
particularly good activity as **phosphodiesterase inhibitors.**
SUMM . . . ischaemia and are therefore useful in the treatment of cerebral
vascular and neuronal degenerative disorders associated with learning, memory and **cognitive** dysfunctions including cerebral senility, multi-infarct dementia, senile dementia of the Alzheimer type, age associated memory impairment and certain disorders associated. . .
SUMM . . . in the prophylaxis of disorders associated with neuronal degeneration resulting from ischaemic events, including cerebral ischaemia due to cardiac arrest, **stroke** and also after cerebral ischaemic events such as those resulting from surgery and/or during childbirth. In addition treatment with the. . .
SUMM . . . formula (I) or where appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as a **phosphodiesterase inhibitor.**
SUMM . . . for use in the treatments mentioned hereinbefore, such as cerebral vascular and neuronal denerative disorders associated with learning, memory and **cognitive** dysfunctions, peripheral vascular disease or proliferate skin disease or for the prophylaxis of disorders associated with neuronal degeneration resulting from. . .

L7 ANSWER 12 OF 21 USPATFULL
PI US 5395844 19950307 <--
DETD . . . or bypass surgery, vascular hypertrophy and hyperplasia, atheroma and Raynaud's disease; cerebrovascular disorders such as

migraine, and ischemic and hemorragic **stroke**; renal disorders such as renal vascular hypertension, proteinuria of primary renal disease, end stage renal disease and renal transplant therapy, glomerulonephritis, nephrotic syndrome, scleroderma and glomerular sclerosis, and for enhancing renal blood flow; CNS disorders such as impairment of **cognitive** function and memory loss, addiction, anxiety, bulimia, depression, epilepsy, pain, Parkinson's disease, psychosis, sleep disorders and tardive dyskinesia; ocular disorders. . .

DETD . . . of congestive heart failure include, in addition, compounds of this invention with cardiac stimulants such as dobutamine and xamoterol and **phosphodiesterase inhibitors** including amrinone and milrinone.

AB Novel substituted imidazoles of Formula (III), which are useful as angiotensin-II antagonists, are disclosed: ##STR1## These compounds, exemplified by the compound 1-((2'-((i-Amyloxycarbonylamino)sulfonyl)-3-

fluoro-(1,1'-biphenyl)-4-yl)methyl)-5-[2-(N-butyryl-N-pyridin-3-ylamino) ethylcarbonyl]-4-ethyl-2-propyl-1H-imidazole, are useful as antihypertensive agents.

L7 ANSWER 13 OF 21 USPATFULL

PI US 5376666 19941227 <--

DETD . . . or bypass surgery, vascular hypertrophy and hyperplasia, atheroma and Raynaud's disease; cerebrovascular disorders such as migraine, and ischemic and hemorragic **stroke**; renal disorders such as renal vascular hypertension, proteinuria of primary renal disease, end stage renal disease and renal transplant therapy, glomerulonephritis, nephrotic syndrome, scleroderma and glomerular sclerosis, and for enhancing renal blood flow; CNS disorders such as impairment of **cognitive** function and memory loss, addiction, anxiety, bulimia, depression, epilepsy, pain, Parkinson's disease, psychosis, sleep disorders and tardive dyskinesia; ocular disorders. . .

DETD . . . of congestive heart failure include, in addition, compounds of this invention with cardiac stimulants such as dobutamine and xamoterol and **phosphodiesterase inhibitors** including amrinone and milrinone.

AB Novel heterocycle substituted azocycloalkane benzylimidazoles of Formula (I), which are useful as angiotensin-II antagonists, are disclosed: ##STR1##

L7 ANSWER 14 OF 21 USPATFULL

PI US 5362915 19941108 <--
WO 9115451 19911017 <--

SUMM . . . ischaemia and are therefore useful in the treatment of cerebral vascular and neuronal degenerative disorders associated with learning, memory and **cognitive** dysfunctions including cerebral senility, multi-infarct dementia, senile dementia of the Alzheimer type, age associated memory impairment and certain disorders associated. . .

SUMM . . . in the prophylaxis of disorders associated with neuronal degeneration resulting from ischaemic events, including cerebral ischaemia due to cardiac arrest, **stroke** and also after cerebral ischaemic events such as those resulting from surgery and/or during childbirth. In addition treatment with the. . .

SUMM . . . a method of treatment in mammals, including humans, of cerebrovascular disorders and/or neuronal degenerative disorders

associated with learning, memory and **cognitive** dysfunctions, including cerebral senility, multi-infarct dementia and senile dementia of the Alzheimer type, which comprises administering to the sufferer an.

. .

SUMM . . . the manufacture of a medicament for the treatment of cerebral vascular and neuronal degenerative disorders associated with learning, memory and **cognitive** dysfunctions including cerebral senility, multi-infarct dementia and senile dementia of the Alzheimer type and/or disorders resulting from an ischaemic event. . .

DETD . . . 118; KCl, 4.6; NaHCO.sub.3, 24.9; KH.sub.2 PO.sub.4, 1; BSA, 0.2 mg/ml. Cells are treated with various concentrations of test compounds (**PDE inhibitors**) for 1 rain before the addition of a threshold concentration of PGE.sub.2 (0.1 .mu.M). Four minutes after the addition of. . .

AB A compound of formula (I) or a pharmaceutically acceptable salt thereof:

##STR1## wherein: R.sub.1 is --CH.sub.3 or --CH.sub.2 CH.sub.3 unsubstituted or substituted by 1 to 3 fluorines;

X is O or S(O).sub.s where s=0 to 2;

R.sub.2 is C.sub.4 -C.sub.6 cyclic alkyl, optionally substituted by one to three methyl groups or one ethyl group; --CH.sub.2 -cyclopentyl, --CH.sub.2 -cyclopropyl, 3-tetrahydrofuranyl, C.sub.1-7 alkyl, CH.sub.3 or CH.sub.2 CH.sub.3 substituted by one to three fluorines;

--(CH.sub.2).sub.n COO(CH.sub.2).sub.g CH.sub.3, or (CH.sub.2).sub.n O(CH.sub.2).sub.g CH.sub.3, wherein n is 2 to 4 and g is 0 to 2;

R.sub.3 represents a moiety of formula (a); ##STR2## wherein R.sub.4 and R.sub.5 each represent hydrogen or R.sub.4 and R.sub.5 together represent a bond;

B represents >C.dbd.O, >C.dbd.S or >CH--R.sub.6 wherein R.sub.6 represents H, OH, C.sub.1-6 alkoxy or C.sub.1-6 thioalkoxy; and m and r each independently represents zero or an integer in the range of 1 to 4 wherein m+r represents an integer in the range of from 2 to 4; with the proviso that when R.sub.1 is methyl, X is oxygen, R.sub.2 is methyl or cyclopenyl, R.sub.3 does not represent cyclopent-1,2-ene-3-one.

L7 ANSWER 15 OF 21 USPATFULL

PI US 5321029 19940614 <--

SUMM . . . compounds are therefore useful in the treatment of cerebral vascular disorders and neuronal degenerative disorders associated with learning, memory and **cognitive** dysfunctions including cerebral senility, multi-infarct dementia and senile dementia of the Alzheimer type.

SUMM . . . in the prophylaxis of disorders associated with neuronal degeneration resulting from ischaemic events, including cerebral ischaemia due to cardiac arrest, **stroke** and also after cerebral ischaemic events such as those resulting from surgery and/or during childbirth. In addition treatment with the. . .

SUMM The compounds of the present invention also act as **phosphodiesterase inhibitors** and elevate cyclic AMP levels and are therefore of potential use in the treatment of proliferative skin disease in human. . .

SUMM . . . a method of treatment in mammals, including humans of cerebral vascular and neuronal degenerative disorders associated with learning,

memory and **cognitive** dysfunctions including cerebral senility, multi-infarct dementia and senile dementia of the Alzheimer type, which comprises administering to the sufferer an. . .

SUMM Relevant ischaemic events include cerebral ischaemia caused by cardiac arrest and by **stroke** and also includes the cerebral ischaemia which may result from surgery.

SUMM . . . acceptable salt thereof, for use in the treatment of cerebral vascular and neuronal degenerative disorders associated with learning, memory and **cognitive** dysfunctions including cerebral senility, multi-infarct dementia and senile dementia of the Alzheimer type and/or disorders resulting from an ischaemic event. . .

SUMM . . . the manufacture of a medicament for the treatment of cerebral vascular and neuronal degenerative disorders associated with learning, memory and **cognitive** dysfunctions including cerebral senility, multi-infarct dementia and senile dementia of the Alzheimer type and/or disorders resulting from an ischaemic event. . .

AB A compound of formula (I): ##STR1## or where appropriate a pharmaceutically acceptable salt thereof, wherein R.sup.1 and R.sup.2 each independently represent a moiety of formula (a):

--(CH.sub.2).sub.m --A (a)

wherein m represents zero or an integer 1, 2 or 3, A represents a substituted or unsubstituted cyclic hydrocarbon radical; and

R.sup.3 represents hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl or a moiety of formula (a) as defined above; a pharmaceutical composition comprising such a compound a process for preparing such a compound and the use of said compound and said composition in medicine.

L7 ANSWER 16 OF 21 USPATFULL

PI US 5308846 19940503 <--

SUMM . . . invention is also concerned with the use of the novel compounds in the treatment of certain CNS disorders such as **cognitive** dysfunction.

DETD . . . of the right eye and down the spinal column. The rats were immediately placed on a Harvard Roden Ventilator (rate--60 **strokes** per minute, volume--1.1 cc per 100 grams body weight). The right carotid artery was ligated, both left and right vagal. . .

DETD . . . of congestive heart failure include, in addition, compounds of this invention with cardiac stimulants such as dobutamine and xamoterol and **phosphodiesterase inhibitors** including amrinone and mirinone.

DETD **COGNITIVE** FUNCTION ASSAY

DETD The efficacy of these compounds to enhance **cognitive** function can be demonstrated in a rat passive avoidance assay in which cholinomimetrics such as physostigmine and nootropic agents are. . .

DETD In order to obtain maximal enhancement of **cognitive** function, the compounds of this invention may be combined with other **cognition**-enhancing agents. These include acetylcholinesterase inhibitors such as heptylphysostigmine and tetrahydroacridine (THA; tacrine), muscarinic agonists such as oxotremorine, inhibitors of angiotensin-converting. . .

AB Substituted quinazolinones and pyridopyrimidines of structural formula 1

##STR1## are angiotensin II antagonists useful in the treatment of

disorders related to the renin-angiotensin system (RAS) such as hypertension, congestive heart failure, ocular hypertension and certain CNS disorders.

L7 ANSWER 17 OF 21 USPATFULL
PI US 5256667 19931026 <--
SUMM . . . invention is also concerned with the use of the novel compounds
in the treatment of certain CNS disorders such as **cognitive** dysfunction.
SUMM . . . of the right eye and down the spinal column. The rats were immediately placed on a Harvard Rodent Ventilator (rate--60 **strokes** per minute, volume--1.1 cc per 100 grams body weight). The right carotid artery was ligated, both left and right vagal. . .

SUMM . . . of congestive heart failure include, in addition, compounds of this invention with cardiac stimulants such as dobutamine and xamoterol and **phosphodiesterase inhibitors** including amrinone and mirinone.
SUMM **COGNITIVE** FUNCTION ASSAY
SUMM The efficacy of these compounds to enhance **cognitive** function can be demonstrated in a rat passive avoidance assay in which cholinomimetics such as physostigmine and nootropic agents are. . .
SUMM In order to obtain maximal enhancement of **cognitive** function, the compounds of this invention may be combined with other **cognition**-enhancing agents. These include acetylcholinesterase inhibitors such as heptylphysostigmine and tetrahydroacridine (THA; tacrine), muscarinic agonists such as oxotremorine, inhibitors of angiotensin-converting. . .
AB Substituted quinazolinones and pyridopyrimidines of structural formula I

##STR1## are angiotensin II antagonists useful in the treatment of disorders related to the renin-angiotensin system (RAS) such as hypertension, congestive heart failure, ocular hypertension and certain CNS disorders.

L7 ANSWER 18 OF 21 USPATFULL
PI US 5223504 19930629 <--
WO 9109859 19910711 <--
SUMM The phosphodiesterases (PDE) are the enzymes responsible for the destruction of cyclic nucleotides and like stimulants of nucleotide cyclases, **PDE inhibitors** also increase levels of cyclic AMP and are effective as bronchodilators, vasodilators, cardiac stimulants, etc.
SUMM Many xanthine derivatives, such as theophylline, have been described as **PDE inhibitors**, however, its lack of selectivity against the different types of PDE is be one reason for the undesirable side effect. . .
SUMM . . . in combatting such other conditions wherein inhibition of PDE type IV is thought to be beneficial, such as depression, impaired **cognition**, rheumatic and other inflammatory diseases, **stroke**, heterograft rejection and other immune related diseases.
AB Xanthines of the general formula: ##STR1## wherein R.sup.1 represents a straight or branched chain alkyl, alkenyl or alkynyl group of 3-6 carbon atoms, and R.sup.2 and R.sup.3, which may be the same or different, each represent hydrogen or halogen or a methyl, methoxy, nitro or trifluoromethyl group or R.sup.2 and R.sup.3 together form a methylenedioxy or ethylenedioxy group; with the proviso that R.sup.2 and

R.sup.3 are not both hydrogen; and pharmacologically acceptable salts thereof with an alkali metal base or a nitrogen base containing organic base, are bronchodilators making them of value in treating asthma and vasodilators making them of interest in treating angina, hypertension, congestive heart failure and multi-infarct dementia. The compounds are also of use in combatting other conditions where inhibition of PDE type IV is thought to be beneficial. The compounds can be prepared by treating and corresponding 6-amino uracil with sodium nitrite and formic
acid in an excess of formamide and adding sodium dithionate to reduce the resulting 6-amino-5-nitroso compound to give the 5,6-diamino compound that ring closes with the excess of formamide.

L7 ANSWER 19 OF 21 USPATFULL
PI US 5202322 19930413 <--
SUMM . . . invention is also concerned with the use of the novel compounds
in the treatment of certain CNS disorders such as **cognitive** dysfunction.
DETD . . . of the right eye and down the spinal column. The rats were immediately placed on a Harvard Rodent Ventilator (rate--60 **strokes** per minute, volume--1.1 cc per 100 grams body weight). The right carotid artery was ligated, both left and right vagal. . .

DETD . . . of congestive heart failure include, in addition, compounds of this invention with cardiac stimulants such as dobutamine and xamoterol and **phosphodiesterase inhibitors** including amrinone and mirinone.
DETD **COGNITIVE** FUNCTION ASSAY
DETD The efficacy of these compounds to enhance **cognitive** function can be demonstrated in a rat passive avoidance assay in which cholinomimetics such as physostigmine and nootropic agents are. . .
DETD In order to obtain maximal enhancement of **cognitive** function, the compounds of this invention may be combined with other **cognition**-enhancing agents. These include acetylcholinesterase inhibitors such as heptylphysostigmine and tetrahydroacridine (THA; tacrine), muscarinic agonists such as oxotremorine, inhibitors of angiotensin-converting. . .
CLM What is claimed is:
. . . drug selected from reserpine, minoxidil, guanethidine, hydralazine, hydrochloride and sodium nitroprusside; a cardiac stimulant selected from dobutamine and xamoterol; a **phosphodiesterase inhibitor** selected from amrinone and milrinone or combinations of the above-named drugs.

AB Substituted quinazolinones and pyridopyrimidines of structural formula 1

##STR1## are angiotensin II antagonists useful in the treatment of disorders related to the reninangiotensin system (RAS) such as hypertension, congestive heart failure, ocular hypertension and certain CNS disorders.

L7 ANSWER 20 OF 21 USPATFULL
PI US 5177085 19930105 <--
DETD . . . through V [Beavo et al., TIPS 11, 150-155 (1991) and Nicholson et al ., TIPS 12, 19-27 (1990)]. Tpye III **PDE inhibitors** are known to be relaxants of human airways smooth muscle. Type IV **PDE inhibitors** are reported to have potent anti-inflammatory actions [Murray et al. Agents and Actions Supplements 34, 27-46 (1991)]. Moreover, elevation of. . .

DETD Having regard to their profile in relation to inhibition of PDE isoenzymes, in particular their profile as type IV **PDE inhibitors**, COMPOUNDS I, ESTERS AND P.A. SALTS are also indicated for use as type IV **PDE inhibitors**, for example: for the treatment of inflammatory and allergic diseases such as rhinitis, conjunctivitis, atopic dermatitis, urticaria and gastro-intestinal allergies;. . . the treatment of other conditions where PDE IV inhibition is indicated, for example, depression, conditions and diseases characterized by impaired **cognitive** function including Alzheimer's disease, Parkinson's disease, rheumatic and other inflammatory disease, **stroke**, heterograft rejection and other immune related diseases, in particular autoimmune diseases such as autoimmune hematological disorders (including e.g. hemolytic anemia,. . .

AB 6,7-Di(C.sub.1-4 alkoxy)-1-[3,5-di(C.sub.1-4 alkoxy)phenyl]-3,4-dihydro-3-hydroxy-methyl-isoquinolines, their physiologically hydrolyzable and -acceptable esters and acid addition salts thereof are novel. The said compounds and esters and pharmaceutically acceptable acid addition salts thereof are useful as pharmaceuticals, e.g. in the treatment of asthma.

L7 ANSWER 21 OF 21 USPATFULL

PI US 5175164 19921229 <--

SUMM The compounds of this invention have central nervous system (CNS) activity. They are useful in the treatment of **cognitive** dysfunctions including Alzheimer's disease, amnesia and senile dementia.

These compounds also have anxiolytic and antidepressant properties and are therefore, useful. . .

DETD . . . of the right eye and down the spinal column. The rats were immediately placed on a Harvard Rodent Ventilator (rate--60 **strokes** per minute, volumn--1.1 cc per 100 grams body weight). The right carotid artery was ligated, both left and right vagal. . .

DETD . . . of congestive heart failure include, in addition, compounds of this invention with cardiac stimulants such as dobutamine and xamoterol and **phosphodiesterase inhibitors** including amrinone and mirinone.

DETD **COGNITIVE** FUNCTION ASSAY

DETD The efficacy of these compounds to enhance **cognitive** function can be demonstrated in a rat passive avoidance assay in which cholinomimetics such as physostigmine and nootropic agents are. . .

DETD In order to obtain maximal enhancement of **cognitive** function, the compounds of this invention may be combined with other **cognition** enhancing agents. These include acetylcholinesterase inhibitors such as heptylphysostigmine and tetrahydroacridine (THA; tacrine), muscarinic agonists such as oxotremorine, inhibitors of. . .

CLM What is claimed is:

12. A method of treating **cognitive** dysfunction, anxiety, or depression comprising administering to a patient in need of such treatment, a therapeutically effective amount of a. . .

AB Substituted heterocycles attached through a methylene bridge to novel substituted indole or dihydroindole derivative of the Formula I are useful as angiotensin II antagonists. ##STR1##

1: Stroke 1997 Apr;28(4):722-8

Task-related training improves performance of seated reaching tasks after stroke. A randomized controlled trial.

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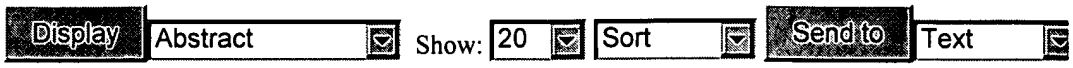
BACKGROUND AND PURPOSE: After stroke, the ability to balance in sitting is critical to independence. Although impairments in sitting balance are common, little is known about the effectiveness of rehabilitation strategies designed to improve it. The purpose of this randomized placebo-controlled study was to evaluate the effect of a 2-week task-related training program aimed at increasing distance reached and the contribution of the affected lower leg to support and balance. METHODS: Twenty subjects at least 1 year after stroke were randomized into an experimental or control group. The experimental group participated in a standardized training program involving practice of reaching beyond arm's length. The control group received sham training involving completion of cognitive-manipulative tasks within arm's length. Performance of reaching in sitting was measured before and after training using electromyography, videotaping and two force plates. Variables tested were movement time, distance reached vertical ground reaction forces through the feet, and muscle activity. Subjects were also tested on sit-to-stand, walking, and cognitive tasks. Nineteen subjects completed the study. RESULTS: After training, experimental subjects were able to reach faster and further, increase load through the affected foot, and increase activation of affected leg muscles compared with the control group ($P < .01$). The experimental group also improved in sit-to-stand. The control group did not improve in reaching or sit-to-stand. Neither group improved in walking. CONCLUSIONS: This study provides strong evidence of the efficacy of task-related motor training in improving the ability to balance during seated reaching activities after stroke.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 9099186 [PubMed - indexed for MEDLINE]



Mar 17 2003 10:44:0

1: Arch Phys Med Rehabil 1998 May;79(5):497-504 Related Articles, Link

Archives of PMR

Functional task benchmarks for stroke rehabilitation.

Stineman MG, Fiedler RC, Granger CV, Maislin G.

Department of Rehabilitation Medicine, the Leonard Davis Institute for Health Economics, Center for Clinical Epidemiology and Biostatistics, Philadelphia, PA, USA.

OBJECTIVE: To determine typical outcome "benchmarks" for 18 functional tasks in patients undergoing stroke rehabilitation. The benchmarks are intended to serve as points of reference to which the outcomes of patients with similar impairments and degrees of disability can be compared. SUBJECTS: Records from 26,339 stroke patients discharged from 252 inpatient facilities across the United States that submitted 1992 data to the Uniform Data System for Medical Rehabilitation. METHODS: Stroke impairment was detailed as the presence or absence of hemiparesis resulting from stroke and the side(s) of involvement. Within each of five stroke impairment categories, patients were further classified by the Functional Independence Measure-Function-Related Groups (FIM-FRGs) into nine syndromes by degree of disability (admission motor and cognitive FIM scores) and by age. Outcomes were determined for each stroke syndrome at patients' discharge from medical rehabilitation. MAIN OUTCOME MEASURES: Patients' median performance levels on each of the 18 items making up the FIM, length of stay, and community discharge rates. RESULTS: The majority of patients whose admission motor FIM scores were above 37 were able to eat, groom, dress the upper body, and manage bladder and bowel functions independently by discharge. In addition to these tasks, most of those whose motor FIM scores were above 55 were able to dress the lower body, bathe, and transfer onto a chair/bed or toilet. The majority of patients whose initial motor FIM scores were above 62 points and whose cognitive FIM scores were above 30 gained independence in mos tasks, including stair climbing and tub transfers. Community discharge rates ranged from 51.6% for the group of patients with the most severe disabilities to 99.2% for the group with the least severe disabilities. CONCLUSION: Th clinician can apply these benchmarks to guideline development and quality improvement, and in establishing patient goals.

Publication Types:
- Clinical Trial

PMID: 9596388 [PubMed - indexed for MEDLINE]

1: Cochrane Database Syst Rev 2000;(4):CD002842 Related Articles, Link

Cognitive rehabilitation for attention deficits following stroke.

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BACKGROUND: Attention problems occur following stroke and are treated using computerised activities or paper and pencil tasks. OBJECTIVES: To determine the effects of cognitive rehabilitation for attention deficits following stroke. SEARCH STRATEGY: We searched the Cochrane Stroke Group Trials Register, Medline, EMBASE, CINHAL and CLIN PSYCH databases and reference lists from relevant articles. Date of most recent searches: December 1998 SELECTION CRITERIA: Controlled trials of attention training in stroke. Studies with mixed aetiology groups were excluded unless they included more than 75% of stroke patients or separate data were available for the stroke patients. DATA COLLECTION AND ANALYSIS: Two reviewers extracted trial data and assessed trial quality. Reviewers contacted investigators for further details of trials. MAIN RESULTS: Two trials were identified with 56 participants. The two trials showed a benefit of training on measures of alertness and sustained attention Only one trial included a measure of functional independence and this showed no significant effect of training. REVIEWER'S CONCLUSIONS: There is some indication that training improves alertness and sustained attention but no evidence to support or refute the use of cognitive rehabilitation for attention deficits to improve functional independence following stroke.

Publication Types:
- Review
- Review, Academic

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1: Neurol Clin 1993 Feb;11(1):25-57 Related Articles, Link

Elements of cognitive rehabilitation after right hemisphere stroke.

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There are two basic approaches to cognitive training: (1) impairment training and (2) task specific training. Impairment training addresses impairments common to a number of tasks and attempts to offer a general benefit to all of the tasks at once. Task specific training focuses on the impairments that arise in a single task and attempts to improve performance on that task. Impairment training of spatial disorders following right hemisphere stroke has shown some success when curricula are properly designed. The success, however, is quite limited because of normal cognitive constraints and those occurring after brain damage. Task specific training in conjunction with the combined application of various cognitive principles appears more promising, but as yet, only a few studies exist. The neurologic factors are likely to be the same factors that influence recovery. The factors that influence trainability are lesion topography (size and location of the focus plus premorbid atrophy), lesion chronicity, and the presence of additional cognitive impairments (anosognosia, confusion, and abulia). Other interventions that may be beneficial, even for training resistant patients, include behavior modification, cognitive prostheses, and drugs.

Publication Types:
- Review
- Review, Tutorial

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